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A SEVERE TYPE OF HEREDITARY ANEMIA WITH ELLIPTOCYTOSIS

INTERESTING SEQUENCE OF SPLENECTOMY

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THESE cases seem worth reporting for two reasons: the facts that no similar cases appear in the literature, and that there seems to have been an unusual effect of splenectomy in one of the patients.

Case Histories. The subjects of this report are 2 brothers, Jerome and Robert C., coming from a family whose disease history is shown by the family tree in Figure 1. In the 5 generations of which we have record, 19 out of 29 boys born to women in the mother's line of descent have developed a severe anemia. Of these, 16 have died—10 in their first year; one is said to have recovered, and the other 2 are our present patients. No girls have been affected.

The parents' bloods are negative in this generation: the transmission has always been through the unaffected mother. The type of heredity here would seem at first glance to be the same sex-linked type as in hemophilia, but another type, the "sex-influenced" heredity whose common example is pattern baldness, cannot be ruled out on the data we have, and considering information that we have on other patients with elliptocytosis is perhaps the more probable. This type is not dependent on the sex chromosomes, and is recessive in the female and dominant in the male. It can be transmitted by the father directly to his sons. It cannot be distinguished from the sex-linked type in a family like this in which no affected males have lived to have children. (I am indebted to Prof. L. H. Snyder for reminding me of the possibility of sex-influenced heredity here.)

Of these 2 boys, Jerome, the younger, born March 15, 1935, is the more seriously affected, because of susceptibility to respiratory infections which apparently are the cause of exacerbations of the anemia and necessitate frequent transfusions. Robert, born June 23, 1931, lives comfortably on an an average hemoglobin of about 7 gm., is able to take part in the ordinary activities of boys of his age, and was supposed by his family to be in normal health until he was brought in with the other children for blood studies. Most of our data come from our study of Jerome, with Robert serving for comparison since he has what might be looked on as the natural uncomplicated course of the condition.

Jerome was first seen in our clinic on April 5, 1941, having been referred from an out-state hospital where he had recently received 2 transfusions. He had been known to be anemic almost since birth, and had been the recipient

of a variety of ineffective medicaments, but need for transfusion had not been recognized before the present episode. On examination he seemed definitely stunted, weighing less than 40 pounds at 6 years, and exhibited the pallor of a severe anemia without jaundice. He had a slight "hemic" murmur; his spleen was neither palpable nor enlarged to percussion, and there was no indication of liver enlargement. There was no lymphadenopathy. Roentgen ray films of the skeleton showed nothing remarkable. Blood studies showed: Hb., 3.4 gm.; R.B.C., 3.53 million; marked fragmentation; extreme hypochromia; fragility, 0.48 to 0.20 (wide resistance span); quantitative urobilin, 0.69% (34% direct, 58% prompt); no reticulocytes were seen. More than 50% of the erythrocytes were elliptical (Fig. 2). The white cell count was 5100, with normal differential. The urine and stools were negative.

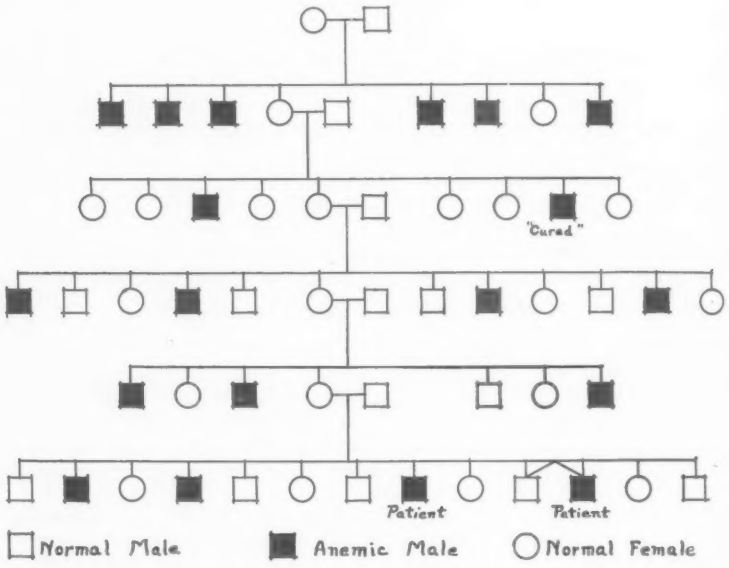

FIG. 1.—Mrs. C's. descent in the female line, which originated in Holland.

Robert was brought in 3 days later for blood study, together with 6 out of 8 siblings, 4 brothers and 2 sisters, all of whom had normal blood, with regard both to anemia and to the presence of elliptocytes. Robert's blood smear resembled Jerome's so closely that it was nearly impossible to distinguish between them; though his hemoglobin was 6.6 gm., there was not the marked fragmentation observed in Jerome's blood, and the blood bilirubin was 0.41%.

Some characteristics of the erythrocytes in these bloods deserve special note, as they differ somewhat from those illustrated in other case reports of "elliptocytic anemia." The most noticeable form in these two bloods is the "sausage" cell, of which there is a high percentage, though at the same time there are many cells recognizable as elliptocytes only as close inspection shows one diameter to be greater than the other. "Pencil cells" are not prominent, nor is the division by median fission so marked as in some types of elliptocytes. A very striking characteristic of the cells, and perhaps the most important, is an appearance of hemoglobin deposition at the periphery of the cell, with complete absence of stain in the center. This "signet ring" appearance has always been prominent in the blood of both boys, and together with the behavior of their counts and the knowledge that there was ample available iron has led us to the belief, to which I shall return later, that the cause

of the anemia lay in an inability to synthesize hemoglobin beyond a certain point. One of my friends said, when this characteristic was described to him, "Whenever the hemoglobin reaches a certain point something seems to put on the brake," which was a good statement of our own opinion of what was happening.

We have observed these 2 boys for more than 3 years. Two other features of their bloods have interested us in addition to those already mentioned. These are the rather frequent occurrence of polycythemia without corresponding rise in the hemoglobin level, and a wide resistance span (*i. e.*, increased maximal resistance with normal or decreased minimal resistance) without the appearance of target cells, which have been supposed to be an explanation for it. As for the polycythemia, Robert has had a number of counts around 6,000,000 and one of 6,500,000, with Hb. in the neighborhood of 7 gm. Jerome's

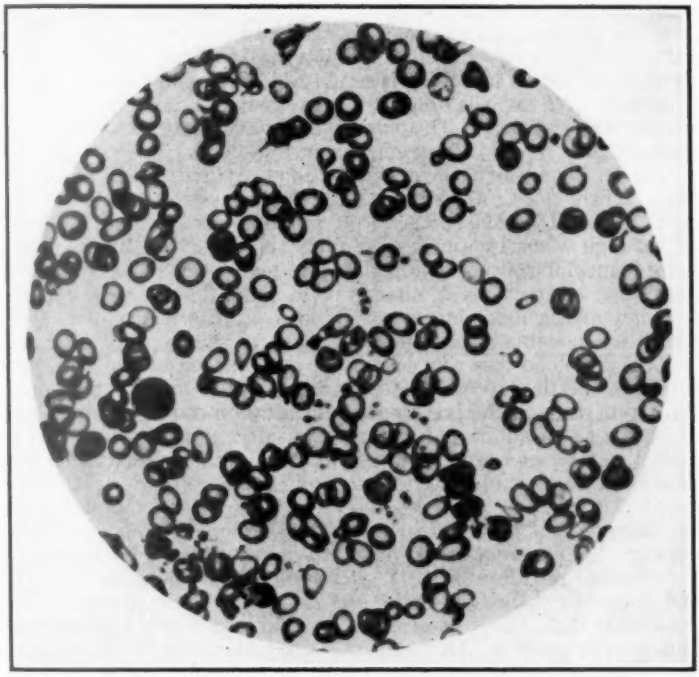

FIG. 2.—Robert C's. blood. There was no perceptible difference between the two bloods. This happens to be our best photograph.

highest count was 6,550,000 and Hb. 6.9 gm. Unfortunately the record does not show hematocrit determinations at these times. This tendency to polycythemia is noticeable in several other reports of elliptocytosis, and implies, of course, a pronounced microcytosis even though the hematocrit reading is lacking.

In February, 1942, a sternal marrow biopsy was performed upon Robert by Dr. W. W. Zuelzer, pathologist. His report (based on the study of both fresh and stained material) describes a cellular marrow in which no abnormalities were observed in cells in the erythroblast or normoblast stages. "The mature erythrocytes are often peculiar in appearance with many elongated and needle-shaped forms. There is also marked variation in the size of the erythrocytes and most of the cells which are not needle-shaped or elliptical in sections appear unusually small." His conclusion reads, "The main

abnormality appears to lie in the appearance and shape of the mature red cells. In the nucleated precursors of these cells, however, no anomalies can be demonstrated in stained sections, and the anomalies of the mature cells are probably better demonstrated in fresh preparations and blood smears than in fixed tissue."

This report adds confirmation to the observation already reported by several writers that the erythrocytes do not take on the elliptical form until just before entering the circulation.

In the course of our studies, Jerome has been the subject of numerous diagnostic and therapeutic tests. His condition was clearly a microcytic, hypochromic anemia of a type which ordinarily would be expected to respond to iron therapy, or perhaps to iron and liver. These drugs, given singly and in various combinations, elicited no response. No reticulocyte rise was ever observed following any of them. In order to eliminate the possibility of failure of iron absorption he was given, in the late spring and early summer of 1942, a series of intravenous injections of colloid iron with no more effect than the oral administration. In July of that year Dr. Carl V. Moore was kind enough to determine for us the boy's serum iron. His report reads: "the serum iron value was 0.246 mg. per 100 cc. . . . . (normal average range for humans is from about 0.060 to 0.180). The only time we have obtained a level as high as 250 micrograms in serum is in pernicious anemia in relapse, in aplastic anemia and with active hemolysis such as occurs with phenylhydrazine therapy in polycythemia. There can be no doubt, therefore, that your boy has an adequate amount of iron and is able, furthermore, to mobilize it from the storehouses. I think the high serum iron means definitely that this youngster is not able to synthesize hemoglobin from iron in the bone marrow." This finding added confirmation to our conclusion, already mentioned, that we were dealing with a form of hypoplasia involving almost exclusively the hemoglobin synthesis. Tests for other possible reasons for an anemia of this type all gave negative results. Occult blood loss was suggested, but nothing of the kind could be found. A hemolytic process was apparently ruled out by the low blood bilirubin value, though the increased fragmentation during relapses was suggestive of this as an additional factor. Considering possible causes for such a hypoplastic state, we were led at once to think of the spleen, which has been suspected by a number of writers of exerting an inhibitory effect on marrow function in the presence of various diseases. Our patient was losing ground, all other therapy had proved futile, and it was finally decided to recommend splenectomy. The parents were slow to consent, but the operation was finally performed on May 25, 1943. The spleen was found to be very large and tied firmly by adhesions under the dome of the diaphragm. This accounted for the fact that we had not been able to detect the enlargement by palpation or percussion; it also had caused surgical difficulties which prevented obtaining blood specimens from the splenic vein as we wished.

Histology of Spleen (Dr. W. W. Zuelzer). It weighed 336 gm. (average normal, 69 gm.). There were no marked variations from normal in the architecture and no increase in fibrous tissue. There were a number of areas of extramedullary hematopoiesis, and it was in the young erythrocytes in these areas that the most striking picture was observed, both in sections and better in imprints stained with Giemsa. There were many cells smaller than normal, and of these a large proportion were elongated or elliptical in shape. These cells were remarkable in that there was a large number, even with no trace of nucleus or nuclear fragments, as well as many cell fragments, which showed no eosin stain whatever, the cytoplasm staining a delicate blue with a pale center. Erythrophagocytosis was observed only rarely. Dr. Zuelzer's conclusion is "Extramedullary hemopoiesis and hyperplasia of spleen. The material suggests formation of red cells which are deficient in hemoglobin as well as abnormal in shape and tend to be fragmented in the spleen."

The immediate effect of the operation was rather surprising. There was a temporary rise in hemoglobin, of brief duration and probably due to massive transfusions preparatory to operation. The unexpected thing was a definite

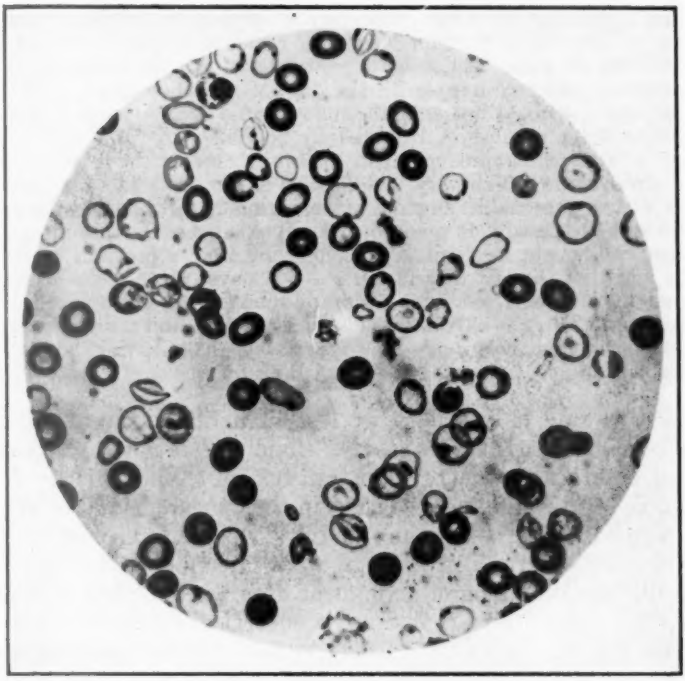

FIG. 3.—Jerome's blood 3½ months after splenectomy. Note two different types of cells.

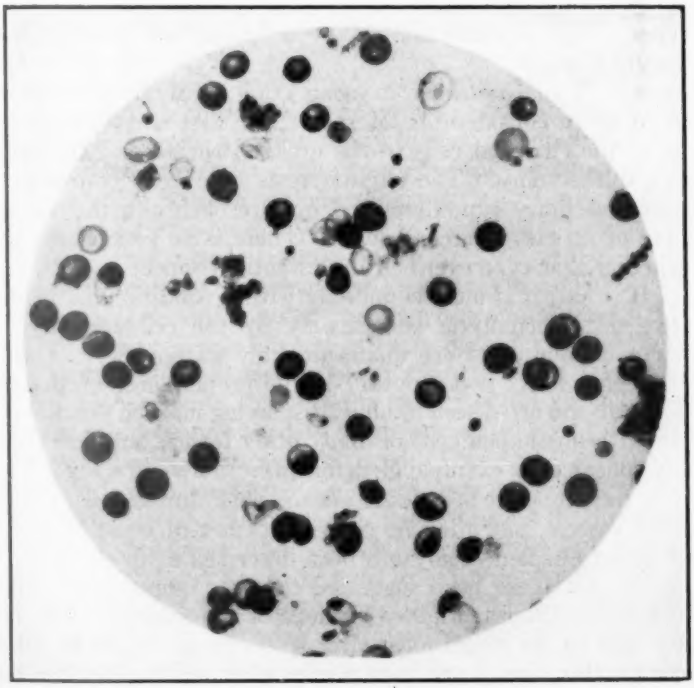

FIG. 4.—Jerome's blood 9 months after splenectomy: 104 days after last transfusion.

tendency to diminution of the proportion of elliptocytes to round forms and an apparent increase in the number of pale blue staining cells without hemoglobin. Both of these tendencies were observed almost immediately after the operation, and continued until the date of the photograph in Figure 3, in which may be noted not only the many round cells without hemoglobin, but a remarkable number of Howell-Jolly bodies. After this date followed a period of apparent improvement in the appearance of the cells. Figure 4, from a smear made in February, 1944, seems to show a fairly high percentage of cells with a reasonable amount of hemoglobin, contrasted with the cell shadows still to be seen. It would be natural to suppose that the more normal appearing cells might be donor's cells surviving from a previous transfusion, but the fact that the last transfusion was 104 days before seems to preclude this possibility. The appearance of improvement in the smear was deceptive, however, as the Hb. was only 5.4 gm., hematocrit 19.8, and reticulocytes 0.5%. No erythrocyte count was made that day, but on the following day, following transfusion of 285 cc. (red cells from the A.R.C.), it was only 1,960,000.

After this date in February we lost sight of the boys until May, as the parents took them to another clinic. Here Jerome apparently received no other treatment than transfusion. When we saw him in the middle of May the improvement in the appearance of his erythrocytes seemed to be continuing, and his Hb. had reached 11.3 gm. (last transfusion early in April). A week later it was 10.9 gm. This looked like the beginning of permanent improvement; but on a recent visit to the clinic after an absence of several weeks he was found to have Hb. 4.4 gm., R.B.C. 1,720,000, W.B.C. 16,000, and reticulocyte count 8.8%. Dr. Zuelzer found that he still had the extremely pale, shadow-like cells with Howell-Jolly bodies on the one hand and fairly normal appearing cells on the other with no transition between the two types. This examination is the only one we have showing a reticulocyte increase.

Comment. Two questions in connection with these cases have seemed to me of considerable interest. The first one is the probable relation of the elliptical cells to the anemia, the second the effect of Jerome's splenectomy. The elliptocytosis here is of course not the dominant hereditary type described by Dresbach and the subject of a number of articles in recent years. There is no general agreement as to whether that type ever has any essential connection with anemic states. If it has, it is most commonly with a condition distinguished from congenital hemolytic icterus only by the cell anomaly. The elliptocytes in our cases are unquestionably pathologic, but are not to be thought of as "poikilocytes" in the proper sense of that term. Elliptical cells are often seen in blood displaying marked poikilocytosis, together with misshapen cells of many other forms, but here they are the only conspicuous example of deformity. There are a good many reports in the literature of cases of anemia with similar cells, especially by Italian writers, but often no evidence of heredity is adduced, and no such effect of splenectomy has been described as in our case.

It has several times been suggested that the elliptocytosis may be an effect rather than a primary element of the anemia. The return of many cells to the round form after splenectomy might be taken as evidence for this view if one were a subscriber to the plausible theory

advanced by Dameshek and others that some splenic effect is responsible for the spherocytes of hemolytic anemia. In that case, I think one could account for the two wholly different types of cells in Jerome's recent blood pictures by supposing that the hematopoietic apparatus of the whole body was involved in the process, and that removal of the spleen remedied only that part of it. This explanation offers a reasonable analogy to what is occasionally observed in other conditions which are benefited but not finally cured by splenectomy.

One more comment seems worth making. This anemia adds one more to the list of the "refractory" anemias, uninfluenced by any form of therapy, except occasionally by splenectomy, and it is noteworthy that, so far as I know, all of these refractory anemias are due to fundamental constitutional defects in the hematopoietic system. Sickle cell anemia, Mediterranean anemia and a familial anemia reported by Strauss and Daland, are other examples. This last, judging from the microphotographs accompanying the report, is also characterized by elliptocytes.

Summary. I have described an anemia observed in 2 brothers, whose family history indicates that the disease is transmitted by unaffected females in the "sex-linked" manner of hemophilia, or the "sex-influenced" manner of pattern baldness, between which it is not possible to distinguish on present information. Both of the brothers exhibit in their blood a striking type of elliptocytosis, which is not found in any of the numerous siblings nor in either parent. Of our 2 patients, Robert, the elder, has never shown indications of serious illness, but lives very comfortably on average hemoglobin of 7.8 gm., while Jerome, the younger, has always been more or less of an invalid, stunted, pale, and subject to rather frequent exacerbations of his anemia in which transfusions become necessary. He has had somewhat more than 20 such periods during our 3 years observation of him. Both Jerome's progress and the family history tend to give a somewhat exaggerated impression of the gravity of the fundamental anemia —in Jerome's case because of these secondary lapses, and in the cases of the other children who died because of inadequate therapy, which did not in any case include transfusion.

The blood of both boys has tended to be microcytic and hypochromic, and each has had periods of polycythemia with counts above 6,000,000. Jerome's frequent relapses have apparently been due to infection, and the fact that at these times his blood shows marked fragmentation makes it seem probable that there is a hemolytic element present, though this could be proved only by determinations of total pigment excretion which we were not prepared to make. His episodes of respiratory infection are described by his parents as asthmatic. We suspected bronchiectasis, but failed to demonstrate it by Roentgen ray. They are probably bronchitis. As his parents, who live a long way from the hospital, keep him at home during these periods, we have no definite knowledge of their character. His white cells when we have seen him immediately following a relapse have usually shown a high neutrophil count, above 20,000.

There was no doubt in our minds that the striking change in Jerome's cells was due to the splenectomy. Robert's cells have not at any time shown anything similar. We believe that the operation influenced favorably the fundamental disease process, and that if by suitable prophylaxis we can minimize the infectious element we may hope for something approaching a cure.

THE FREQUENCY OF THALASSEMIA

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In 1942 Wintrobe,[13] commenting on the frequency of thalassemia (Cooley's anemia, erythroblastic anemia, Mediterranean anemia), wrote that "the disease is rare, apparently, for less than 100 cases have been reported since Cooley's paper appeared in 1925." Recently we have collected data indicating that the disease is more common than the number of published reports would indicate. As is well known, the condition is largely confined either to peoples now living on or near the shores of the Mediterranean—Greeks, Italians, Syrians, Armenians—or to those whose ancestors lived there until recent times. This report is an attempt to estimate the incidence of the condition in one specific group derived from the Mediterranean region, namely, individuals of Italian descent residing in the city of Rochester, N. Y. These individuals are for the most part either immigrants from Sicily and southern Italy or the descendants of such immigrants, and so represent a relatively homogeneous element. Such an estimate not only has some medical interest but is basic to an estimation of the frequency of a related but milder anemia to be discussed below.

Table 1 summarizes the known cases of thalassemia occurring in individuals of Italian descent born in the city of Rochester, N. Y., between 1928 and 1942 and admitted to the various hospitals of this city. The year 1928 has been arbitrarily chosen as the beginning point in this series because, although the disease was first described in 1925, a certain lag in the general recognition of the condition is unavoidable. The year 1942 has been chosen as the last year because cases are often not recognized prior to 1 year of age, so that some cases born subsequent to this date may not yet have come to the attention of a physician. We are very grateful to the various hospitals of this city for their coöperation in permitting us to examine their records of cases of thalassemia. Eleven individuals with the disease are known to have been born in this city over the 15-year period. This figure is probably a minimum estimate of the number of cases, since some individuals

may go undiagnosed and die at an early age of intercurrent infection, to which they are very susceptible.

TABLE 1.—CASES OF THALASSEMIA BORN IN ROCHESTER BETWEEN 1928 AND 1942 AND DIAGNOSED IN THE VARIOUS HOSPITALS OF THE CITY

Hospital	No. of cases
Strong Memorial and Rochester Municipal Hospitals	5
The Genesee Hospital	3
Rochester General Hospital	2
Highland Hospital	1
St. Mary's Hospital	0*
Park Avenue Hospital	0
	11

* The case described by Flynn[6] from St. Mary's Hospital was not a native of Rochester.

Rochester has a relatively large Italian population. At the time of the 1930 census, there were 23,935 individuals in Rochester who were born in Italy, and 31,478 first generation native whites born of Italian or mixed Italian parentage.[2] The 1940 census figures are less useful, since the number of first generation Italians is not listed; the number of persons born in Italy is given as 20,929.[3] The number of second generation Italians can only be approximated; various approaches lead to an estimate of an average of 20,000 living in this city between 1928 and 1942. These figures lead to the estimate that in the years 1928–1942 there was an average of approximately 75,000 individuals Italian born or of Italian descent in this city. Maller,[8] on the basis of the 1930 census figures and vital statistics data for 1930 secured from the Department of Health of New York City, found that the mean birth rate for 15 Italian areas in New York City for the year 1930 was 23.15 per 1000. The birth rate is probably not greatly dissimilar in the Italian areas of Rochester. Over the 15-year period from 1928 to 1942 one can, on the basis of these figures, reasonably estimate the number of children born of Italian parentage as 26,044. The incidence to thalassemia is therefore approximately 1 in 2368 births, or 0.00042. Stevens[10] has pointed out that when dealing with such small fractions, one cannot employ the usual formula for estimating the error of a proportion ($\sqrt{p(1-p)/n}$) but should use a method, which he describes, based upon an expansion of the binomial series. By this latter method, the probability is 19 in 20 that the "true" frequency of thalassemia lies between 0.00021 and 0.00076. This method makes allowance for differences between the observed and the "true" frequency due to the sampling technique, but does not, of course, take into account possible inaccuracies in the estimate due to differences between the actual and estimated size of the Italian element and its birth rate.

In 1940 and 1941 three groups of investigators[4,11,14] independently described a new type of familial, iron-resistant, hypochromic, microcytic anemia occurring in individuals of Italian descent. They pointed out that this anemia was qualitatively similar to thalassemia but was quantitatively much less severe in that it lacked the degree of red cell imperfection and circulating erythroblasts. Wintrobe[13] subsequently showed that both the parents of 2 individuals suffering from thalassemia

had this similar but milder anemia. Dameshek[5] and Smith[9] confirmed this observation and also found the milder condition in siblings of individuals with thalassemia. A number of theories as to the mode of inheritance and relationship of these two anemias were promulgated. The present authors have elsewhere[12] reviewed these theories and found that the available data are best fitted by the hypothesis, first suggested in incomplete form by Caminopetros,[1] that thalassemia is due to homozygosity for an inherited factor, and that the similar, milder disorder is due to heterozygosity for the same factor. In other words, there is, according to genetic hypothesis, a factor which when represented once in the germ plasm results in the mild anemia; when represented twice, in thalassemia. In view of the peculiar etiologic relationships between these two anemias, we[12] have suggested the term "thalassemia major" for full-blown thalassemia, and "thalassemia minor" for the milder disorder.

As yet no direct surveys of the frequency of thalassemia minor in individuals of Italian descent are available. However, given an hereditary mechanism such as has been postulated, the frequency of thalassemia minor can readily be calculated once the frequency of thalassemia major is known. If we let A′ represent the inherited factor responsible for thalassemia, and A its normal allelomorph, then with respect to these factors adult Italians are of two types, AA (normal) and A′A (thalassemia minor). The homozygote A′A′, showing thalassemia major, with rare exceptions dies before the age of reproduction. Let x be the frequency of AA individuals, and y the frequency of A′A. Assuming random mating and equal fecundity for both types, the various possible marriages would occur with the frequencies and results shown in Table 2. The frequency with which children with thalassemia major appear in the Italian population is $\frac{y^2}{4}$. Since the incidence of thalassemia major is estimated at 0.00042, then

$$\frac{y^2}{4} = 0.00042, \text{ and}$$

$$y = 0.041.$$

This indicates that thalassemia minor occurs in approximately 1 in each 25 adult Italians. If the true frequency of thalassemia major is more nearly 0.00021 (the lower estimate given above, compatible with the data at the 5% level of significance), then the frequency of thalassemia minor is 1 in 34, while if the frequency of the major form is 0.00076 (the higher estimate given above, likewise compatible with the data at the 5% level of significance), thalassemia minor would occur in about 1 in 18 individuals. This estimate of the frequency is sufficiently high to make one wonder why the disease has gone so long unrecognized. As has been pointed out by various investigators[5,12] the condition is usually mild and readily confused with an iron-deficiency anemia.

The present estimates of the frequency of thalassemia major and minor can only be regarded as approximate. However, no source of

major error in the calculations is immediately apparent. No allowance is made for the effect of consanguinity on the calculations, the amount of this in the Italian community being unknown. The existence of significant degrees of consanguinity would result in a spuriously high estimate of the frequency of the mild disease. On the other hand, marriages between Italians and other racial elements in which the postulated factor is less common will decrease the incidence of thalassemia major, and hence give a spuriously low estimate of the frequency of thalassemia minor. For the present these two opposing influences are regarded as cancelling each other out in the above calculations. Elsewhere[12] we have pointed out an apparent excess of thalassemia minor in marriages between normal individuals and those with thalassemia minor; this fact does not influence the calculations.

TABLE 2.—THE RESULTS OF RANDOM MARRIAGE IN A POPULATION CONTAINING THE GENOTYPES AA AND A′A IN THE FREQUENCY x AND y

Marriage	Frequency of marriage	Type and frequency of offspring
AA × AA	x^2	x^2AA
AA × A′A	$2xy$	xyAA:xyA′A
A′A × A′A	y^2	$\frac{y^2}{4}$AA:$\frac{y^2}{2}$A′A:$\frac{y^2}{4}$A′A′

Persons having the constitution A′A′ are not included in the calculations since in this case such individuals rarely reproduce.

The clinical significance of thalassemia minor has yet to be evaluated carefully. Many persons compensate for their individually deficient erythrocytes by an increased red cell count, and therefore they have approximately normal values for hemoglobin and hematocrit. Others fail to make this adjustment, and go through life with subnormal values. It seems probable that they are handicapped to the same extent as individuals with an iron-deficiency anemia of comparable magnitude (Mackay[7]), with the added disadvantage that this is a chronic disorder. Further studies on the clinical significance of a disease involving approximately 4% of individuals of southern Italian extraction are desirable.

Summary. From a survey of hospital records, the incidence of thalassemia major in the Italian element of the city of Rochester, N. Y., was found to be approximately 0.00042 (1 in each 2368 births). The incidence of the genetically related condition, thalassemia minor, was estimated to be 0.041 (1 case in each 25 persons).

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EOSINOPHILIA FOLLOWING PARENTERAL LIVER THERAPY

Literature and Case Report

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Among the less well known and the less common causes for eosinophilia is the therapeutic administration of liver and liver extract. Although it was realized that eosinophilia occurred not infrequently in cases of untreated pernicious anemia,[5,21] following the introduction of liver therapy for pernicious anemia by Minot and Murphy,[26,27] a number of reports of eosinophilia as a result of treatment with liver appeared in the literature.[4,11,14,29,30,34,35] It early became evident, however, that eosinophilia following the use of liver was not restricted to patients with pernicious anemia, for this finding was frequently observed both in normal subjects and in patients suffering from disorders other than pernicious anemia when liver or liver extract was administered in repeated doses.[1,13,20,31,32] In Table 1 are summarized the cases of eosinophilia following liver therapy of various types which we have been able to gather from a careful survey of the literature to date (June 1944).

The most extensive papers on the phenomenon of eosinophilia following the therapeutic use of liver are those of Meulengracht and Holm,[25] Massobrio and Maranzana,[23] and Allin and Meyer.[2] In 1930, Meulengracht and Holm[25] studied the eosinophil count following the administration of raw liver, fried liver, and oral liver extract in a group of patients with pernicious anemia and in a control group of patients suffering from a variety of other diseases. In both groups of subjects identical changes were found. The daily administration of large doses of raw liver resulted regularly in marked eosinophilia which in 1 case reached a level of 74%. As a rule, the eosinophilia appeared rather suddenly after about 4 weeks of treatment, and it persisted as long as the administration of raw liver was maintained. In those patients who received repeated doses of fried liver or oral liver extract eosinophilia occurred only occasionally and in no instance was higher than 9%.

Massobrio and Maranzana,[23] in 1938, extensively reviewed the literature on the subject of eosinophilia following the ingestion of liver and added a number of case studies of their own. They found that in a series of 17 patients with pernicious anemia who were treated by the

daily administration of steamed liver eosinophilia appeared in 12 instances, reaching a level of over 20% in 2 cases; 2 of the 5 patients who showed no eosinophil response were followed for only 2 weeks. The authors observed that in the majority of instances the eosinophilia made its appearance about 4 weeks after the institution of liver therapy, although in 2 cases levels of 12 and 14% were present after only 1 week. In a group of 4 pernicious anemia patients who were treated by the

TABLE 1.—A TABULATION OF REPORTED CASES OF EOSINOPHILIA FOLLOWING THE ADMINISTRATION OF LIVER OR LIVER EXTRACT

Year	Author	No. of cases with eosinophilia*	Type of liver	Maximum range of eosinophilia	Type of subjects
1927	Watkins and Berglund[24]	1	Raw	48% of 10,000	P.P.A.
1928	Poulton[30]	1	Raw	3400 per c.mm.	P.P.A.
1928	Whitby[35]	4	Raw or cooked	5–26%	P.P.A.
1928	Ordway and Gorham[29]	1	Raw (?)	25%	P.P.A.
1928	Smith and Whitby[32]	11	Raw	470 to 13,000 per c.mm	Convalescents from diseases other than P.P.A.
1928	Adler and Schiff[1]	2	Oral extract	9%	Normals†
1928	Seyfarth[31]	6	Raw or slightly cooked	9–15%	Normals
		Not specified	Raw or slightly cooked	10–15%	P.P.A.
1930	Fiessinger and Laur[11]	1	Raw	8% of 4800	P.P.A.
1930	Griva[12]	8	Partly cooked	6–51%	P.P.A.
		3	Partly cooked	6–8.5%	Anemias other than P.P.A.
1930	Meulengracht and Holm[25]	22‡	Raw	Up to 74%	P.P.A.
		4	Raw	Up to 67%	Diseases other than P.P.A.
		1	Fried	6%	P.P.A.
		1	Fried	9%	Diseases other than P.P.A.
		2	Oral extract	8–9%	P.P.A.
1932	Lehndorff[20]	1	Raw	45%	Hemolytic anemia
1932	Heilmeyer[14]	2	Parenteral extract	15% of 10,600 19% of 8200	P.P.A.
1933	Barone and Costa[4]	3	Whole liver	10–41%	P.P.A
1935	Corelli[8]	1	Whole liver orally and extract parenterally	28%	Pregnant woman with P.P.A.§
1938	Massobrio and Maranzana[23]	12	Steamed liver	Up to 20%	P.P.A.
		5	Raw	14–27%	P.P.A.
		3	Nearly raw	5–13%	Normal
1939	Murphy[28]	1	Whole liver	50% of 18,000	P.P.A.
1940	Allin and Meyer[2]	10	Cooked	Average 8.6%	P.P.A.
		10	Oral extract	6–10%	P.P.A.
		36	Parenteral extract	Average 11.3% (maximum 36%)	P.P.A.
		31	Mixed oral and parenteral therapy	Average 10.4%	P.P.A.
		1	Parenteral extract	7.75%	Normal
		1	Parenteral extract	9.75%	P.P.A.

* Those cases in which eosinophilia did not develop are not included in this table.
† One dog given fresh liver and a second given liver extract orally showed mild eosinophilia.
‡ This figure may not be correct; the exact number is not set forth in the original report.
§ The new-born infant showed an eosinophilia of 5% at birth; eosinophilia was not present 2 months later, although the child was breast fed.

daily administration of liver boiled at 100° C. for 30 minutes eosinophilia did not result despite good response of the erythrocytes; 1 of these patients was later given raw liver by mouth and within 2 days developed an eosinophilia of 20%. A third series of 9 patients with pernicious anemia received liver extract parenterally for therapy, and in no instance was eosinophilia induced; 4 of this group were then given whole uncooked liver by mouth with resultant eosinophilia of from 14 to 27%. A group of 3 normal subjects was fed nearly raw

liver daily, and within 1 to 2 weeks eosinophilia of from 5 to 13% was observed in each instance and was maintained at about the maximum level as long as liver was continued. The authors found that once eosinophilia following the ingestion of liver appeared it remained as long as treatment was maintained, and that when liver therapy was discontinued the eosinophil level decreased to within normal limits in from 10 to 20 days.

Massobrio and Maranzana fed 4 dogs, in which parasitosis had been excluded, daily rations of raw liver. In each instance an eosinophilia of from 20 to 26% resulted within from 15 to 30 days. Immature and young forms of the eosinophilic granulocyte series were extremely rare in the peripheral blood, a maximum of only 3% of eosinophilic metamyelocytes having been noted. Specimens of bone marrow obtained from the animals during periods when eosinophilia in the peripheral blood was pronounced revealed no significant changes in the numbers of cells of the eosinophilic series.

Allin and Meyer,[2] in 1940, reviewed the records of 279 patients with pernicious anemia. Of 224 who had received liver therapy in one form or another, 87 developed eosinophilia of 4% or more of the total leukocyte count at some time during the period of observation. Eosinophilia was found in 10 of the 13 cases given cooked liver by mouth and in 10 of the 41 patients who received liver extract preparations orally. Of the 79 patients to whom liver extract was given intramuscularly, 36 showed an eosinophilia which averaged 11.3%, the maximum figure being 36%. Of the group of 91 patients who received mixed oral and parenteral therapy, eosinophilia resulted in 31. However, in the group of 55 patients who received no liver therapy eosinophilia occurred in 27 instances.

Allin and Meyer administered repeated doses of liver extract parenterally to 5 previously untreated patients with pernicious anemia and to 4 normal subjects from whom no allergic history could be obtained; mild eosinophilia developed in 1 of the normal subjects and in 1 of the pernicious anemia patients. The 9 patients making up the two groups just mentioned were skin tested with intradermal liver extract before and after the institution of parenteral liver therapy, but the authors could find no correlation between the results of the skin tests and the presence or absence of eosinophilia following the use of liver extract parenterally. They state that it has not been demonstrated that the eosinophilia following liver therapy is allergic in nature, though they admit that this possibility has not been excluded.

It is apparent from an analysis of the available evidence presented so far that eosinophilia is very commonly found after the continued administration of either raw or partially cooked liver. With well-cooked liver and with oral liver extract eosinophilia only occasionally occurs, and when present the level is never high. Reported instances of eosinophilia following the parenteral administration of liver extract are uncommon. Neither Allin and Meyer[2] in 1940, nor Whitby and Britton[36] in 1942, could find any references in the literature to such cases. The only instances of which we have knowledge are those

cases reported by Heilmeyer[14] and by Allin and Meyer.[2] Inasmuch as so few reports have found their way into the medical literature despite the large amounts of liver extract which are being used parenterally in all parts of the world, it would seem that eosinophilia as a result of parenteral administration of liver extract is indeed uncommon.

We have recently had the opportunity to study a patient who developed a marked eosinophilia following the parenteral administration of crude liver extract. Because, to our knowledge, this case represents the most marked eosinophil response to parenteral liver extract which we have encountered in our review of the literature, we are reporting the case in detail.

Case Report. L. V., a white female, 45 years of age, entered the Graduate Hospital, under the care of Dr. Henry Tumen on October 29, 1943, complaining of a generalized papular eruption of 1½ year's duration and jaundice of 1 year's duration. Shortly after the onset of her jaundice the patient noticed that her urine was becoming dark and that her stools were becoming clay colored. There was no history of fever or abdominal pain. Questioning revealed numerous attacks of urticaria in childhood and adolescence, but there was no history of asthma or allergic rhinitis. She was studied in another city and an exploratory laparotomy was advised. At operation, in September 1943, no extrahepatic biliary tract disease was found; the liver was enlarged and its surface presented a number of tiny grayish-blue areas; the spleen was markedly enlarged and was removed. Following surgery the patient's jaundice and pruritic papular eruption persisted.

Examination on admission to the Graduate Hospital revealed a thin white female who was obviously jaundiced. There was no fever or adenopathy. Xanthomatous plaques were scattered over her entire body, being especially noticeable in the palms of the hands and in the region of the outer canthi of her eyes. The lungs were negative, and examination of the heart revealed an apical systolic murmur. Blood pressure was within normal limits. The liver was palpable 3 finger-breadths below the right costal margin and 4 finger-breadths below the xiphoid process in the epigastrium; it was firm and presented a finely nodular surface to palpation. Rectal examination was nonrevealing. No neurologic abnormalities were found.

During her hospital stay repeated urine analyses were negative except for the presence of bile and traces of albumin. The erythrocyte count varied from 3.1 to 4.7 million cells per c.mm., the hemoglobin ranging from 9 to 12 gm. %. Several platelet counts were within normal limits. Occasional target cells were found in the blood smears, but Howell-Jolly bodies were not seen. The total leukocyte and differential counts during the period of hospitalization are graphically presented in Figure 1. The blood sugar was 96 mg. per 100 cc., the alkaline phosphatase 11.8 Bodansky units, and the cholesterol 1608 mg. per 100 cc. The total serum proteins varied from 8.64 to 6.08 gm. % with an albumin component of from 4.85 to 3.45 gm. %. The prothrombin time on repeated occasions ran the gamut from 100% of normal to 27% of normal, and the serum bilirubin ranged from 30 to 4.5 mg. per 100 cc. The cephalin flocculation test was strongly positive.

The patient was placed on a high protein, high carbohydrate, and low fat diet with vitamin supplements, and parenteral glucose was administered daily. The hepatic status gradually improved so that when the patient finally left the hospital on February 16, 1944, the cholesterol had fallen to 594 mg. per 100 cc. with esters of 388; the serum bilirubin level had decreased to 0.8 mg. per 100 cc.; and the xanthomatous plaques, though still present, had largely receded. The diagnosis on discharge was non-obstructive biliary cirrhosis, unverified.

From November 27, 1943, until January 6, 1944, the patient was given a daily intramuscular injection of Lilly's crude liver extract. At no time during

the administration of the liver extract did urticaria, rhinitis, wheezing, or any other manifestations of an allergic nature appear. A blood count on January 5 revealed a leukocytosis of 19,850, with 11,286 eosinophils per c.mm. Because it was thought that this marked eosinophilia might be due to the administration of liver extract, the use of this substance was discontinued. During the succeeding 4 weeks the eosinophilia gradually decreased until on February 7 only 3% of the total leukocyte count of 9550 cells per c.mm. was of the eosinophilic series. That evening the patient was given 2 minims of the crude liver extract intradermally, but no wheal or erythema resulted, and that same evening a single dose of 2 cc. of the crude extract was administered intramuscularly. Fifteen hours later the eosinophils numbered 693 per c.mm., and on the following day there were 2882 eosinophils per c.mm. The changes in the total and differential leukocyte counts throughout the patient's hospital stay are graphically presented in Figure 1. At no time were young or immature cells of the eosinophil series present in the blood smears.

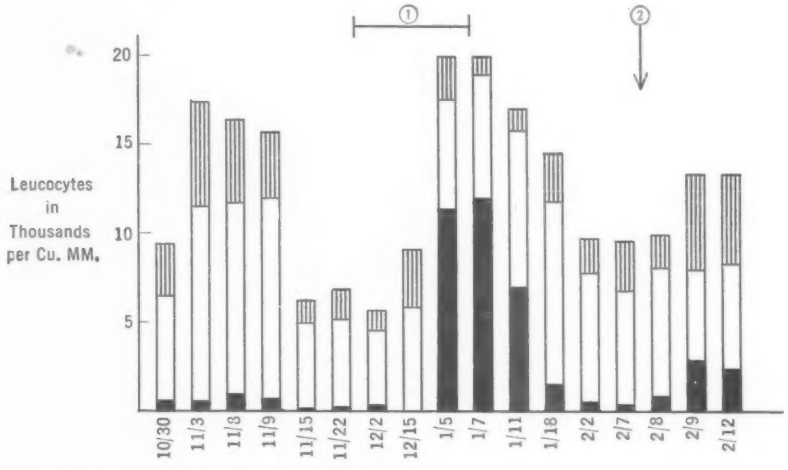

FIG. 1.—A graph of the patient's total leukocyte and differential counts. Solid areas, eosinophils; clear areas, neutrophils; striped areas, lymphocytes, basophils and monocytes. ① Lilly's Crude Liver Extract, 2 cc. I.M., daily from 11/27/43 to 1/6/44. ②, One dose of 2 cc. of Lilly's Crude Liver Extract I.M. on the evening of 2/7/44.

Discussion. The significance of and the mechanism underlying the development of eosinophilia following liver therapy are still matters of surmise. Watkins and Berglund[34] were of the opinion that eosinophilia might represent the reaction of the body to overdosage with liver, whereas Whitby[35] believed that the presence of eosinophilia was a favorable prognostic sign in patients undergoing treatment for pernicious anemia. Barone and Costa[4] observed that eosinophilia did not occur after the administration of raw stomach or stomach extract for pernicious anemia, and they ventured the opinion that the eosinophilia occurring as the result of liver therapy bears no relationship to the presence of the unidentified antipernicious anemia factor. Seyfarth[31] and Griva[13] considered the eosinophilia following liver therapy as an indication of bone marrow stimulation. Meulengracht and Holm[25] regarded it as a harmless phenomenon and felt that it bore no relation to the curative effect of liver in pernicious anemia. Massobrio and Maranzana[23] concluded from their observations that the substance in

liver responsible for the development of eosinophilia was thermolabile in nature, and the presence of eosinophilia in the new-born infant at a time when the mother's blood showed marked eosinophilia, in the case study reported by Corelli,[6] might indicate that the provocative substance may be able to pass through the placental barrier.

Although the mechanism underlying the eosinophil response to liver is not clear, an allergic mechanism has been hypothesized by many as an explanation of this phenomenon. It is of interest in this connection that in none of the reports of eosinophilia following the administration of liver or liver extract which we have reviewed was any mention made of concomitant findings suggestive of or indicative of a clinical allergic state such as asthma, urticaria, shock, etc. On the other hand, a number of reports have appeared in recent years concerning allergic manifestations which have occurred in the course of parenteral liver extract therapy,[7,8,12,16,19] the most recent review article on the subject being that of Kaufman and Farmer.[17] In only one report[3] was mention made of eosinophilia. Since allergic reactions to whole liver, either cooked or raw, or to liver extract by mouth are extremely uncommon as compared with the number of allergic reactions following parenteral liver therapy,[17] and since eosinophilia following whole liver by mouth is much more frequent and much more marked than with parenteral liver extract, it seems logical to us to conclude, as did Epler,[10] that eosinophilia following the administration of liver or liver extract is not related to the development of allergy in any of its known manifestations.

It is of interest that the eosinophilia in our present case report was not accompanied by any clinical manifestations of frank allergy and that the intradermal skin test with the liver extract used was negative. If allergy is to be implicated as the mechanism involved in the production of eosinophilia in this instance, it must necessarily be a monosymptomatic allergy characterized by eosinophilia alone. We have no basis upon which to postulate this.

What rôle the absence of a spleen in our patient may possibly have played in the development of eosinophilia following parenteral liver extract administration must remain a moot question. There is some evidence to show that there is a relationship between the spleen and the number of eosinophils in the circulating blood. Although Ishihari[15] was of the opinion that the spleen had no regulating influence on the eosinophil count in the guinea-pig, Mayr and Moncorps[24] were able to produce eosinophilia in guinea-pigs following splenectomy and were then able to reduce the number of eosinophils in the circulating blood by the injection of protein-free splenic extracts. Instances of eosinophilia following splenectomy in humans are cited by Downey,[9] and Kirk[18] has observed the development of eosinophilia in 5 of 8 patients who were subjected to splenectomy.* He found that eosinophilia occurred as early as the 6th postoperative week and persisted for as long as 38 months. Waldbott[33] has postulated that hypofunction of the spleen results in eosinophilia, whereas hyperfunction of the spleen

* A postsplenectomy eosinophilia (6 to 20%), after complete disappearance for several weeks beginning about the third postoperative week, was observed by us[29a] in normal dogs many years ago.—EDITOR.

gives rise to hypo-eosinophilia, and Whitby and Britton[36] state that some weeks after splenectomy the eosinophils may constitute about 10% of the total numbers of leukocytes. It is conceivable that in the case which we have reported the absence of a spleen may possibly have been a predisposing factor to the development of eosinophilia subsequent to the administration of liver extract parenterally.

Wintrobe[37] makes no mention in his text of liver disease as a cause of eosinophilia, and Lichtman[22] in discussing the changes in the leukocytes which occur in patients with liver disease does not point out any alterations in the eosinophil count. It is, therefore, very unlikely that the presence of severe hepatic damage in our patient had any relation to the eosinophilia which occurred.

Summary. 1. The literature on eosinophilia following liver therapy has been reviewed.

2. Although eosinophilia, often of marked degree, is very commonly found after raw or poorly cooked liver has been administered continually, it is an uncommon finding following the use of well-cooked liver, of oral liver extract, and of parenteral liver extract.

3. The possible rôle of allergy in the development of eosinophilia following liver and liver extract has been briefly discussed, and the relationship between the spleen and eosinophilia has been commented upon.

4. A case of marked eosinophilia following parenteral liver therapy has been presented.

We are indebted to Dr. Henry Tumen for permission to report this case and for his interest during the preparation of this manuscript.

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THE PROGNOSTIC VALUE OF MARROW EOSINOPHILS IN THROMBOCYTOPENIC PURPURA*

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THE value of marrow examination in thrombocytopenic purpura has become well established. By its means, thrombocytopenias have been classified into "secondary" and "primary" types. The former term encompasses a group characterized by the replacement of the marrow by various tissues, a replacement also involving the platelet parent cell—the megakaryocyte. The latter group, on the other hand, apparently has no gross morphologic basis, the megakaryocytes, in the greater number of instances, being present in abundance. It is in these cases that the spleen became incriminated and its "inhibitory" or "thrombolytic" activity made plausible by the dramatic results following its removal.

It was while studying a group of these "primary" thrombocytopenic purpuras that we became impressed by the close correlation between the clinical course and the number of eosinophils in the marrow. In a series of 30 cases here reported, it is shown that increased numbers of eosinophils in the marrow signify a favorable prognosis for spontaneous recovery, while scant numbers foretell a chronic course and the necessity for splenectomy. We believe that the marrow eosinophilia in these cases indicates an allergic state, and that the thrombocytopenia represents a "sensitization" reaction involving the megakaryocytes.

Material and Methods. The 30 cases studied were all typical thrombocytopenic purpuras characterized by marked reduction in the number of platelets, prolongation of the bleeding time, delayed clot retraction, abnormal bleeding from the body orifices, petechiæ and ecchymoses in the skin and mucous membranes, and decreased capillary resistance. The patients ranged in age from $2\frac{1}{2}$ to 64 years. Their histories of purpura anteceded the observation period by from 1 day to 17 years. Marrow was obtained in each instance by aspiration biopsy from the sternum. Direct smear preparations were made and

* Aided by a grant from the Wilson Laboratories, Chicago.

stained in the usual manner with Romanowsky stains. In determining the degree of the eosinophilia it was found that simple percentage figures were subject to considerable variations depending on *relative* increases in other cell types. Therefore, it was deemed advisable to compare the number of the eosinophils with cells of a like character. Since eosinophils presumably arise from the same stem as the neutrophils, and since in the majority of instances no specific stimulation of the granulocytes occurs in thrombocytopenic purpura, we selected these cells as a basis of comparison. Thus, neutrophilic granulocytes in an analogous state of maturation (*i. e.*, metamyelocytes or older) were used as a yardstick. No cells earlier than metamyelocytes were included in either the eosinophil or neutrophil counts, since it was felt that specific granulation in earlier cells might not be unequivocally identified. In each instance the number of eosinophils observed in counting 1000 granulocytes of the neutrophilic series was determined. From 2 to several thousand neutrophils were counted in each case, and rather close agreement was found for each group of 1000 cells done by different observers, suggesting that the counting of 1000 cells will usually suffice. With experience, the impression gained from merely "scanning" the smears will be found to correlate remarkably well with the actual counts, and we have learned to rely much on "impression" in the borderline cases.

TABLE 1.—THE NUMBER OF EOSINOPHILS IN THE BONE MARROW WITH THE PREPONDERANCE OF DEATHS AND CHRONIC PURPURAS IN CASES WITH LESS THAN 50 EOSINOPHILS PER 1000 GRANULOCYTES

Spontaneous recovery		Chronic purpura		Successful splenectomies		Deaths		Disappeared without recovery	
Case No.	Eosinophils per 1000 marrow granulocytes	Case No.	Eosinophils per 1000 marrow granulocytes	Case No.	Eosinophils per 1000 marrow granulocytes	Case No.	Eosinophils per 1000 marrow granulocytes	Case No.	Eosinophils per 1000 marrow granulocytes
				Few Eosinophils in Marrow					
10	38	11	33	13	54, 36	23	26	26	23
		12	32	14	41	24	37		
				15	43, 35, 35	25	44		
				16	22	27	35		
				17	33				
				18	33				
				Many Eosinophils in Marrow					
1	52			19	78				
2	63, 98, 83			20	59				
3	53			21	52, 53				
4	94			22	81				
5	136								
6	83								
7	76								
8	56								
9	50								
28	322								
29	73, 50								
30	133								

The eosinophil counts (per 1000 granulocytes) ranged from 22 to 322. The selection of 50 as the borderline figure was on the basis of experiment alone (Table 1), figures below this occurring in the non-recovery

series, and figures above this being found in those with spontaneous recoveries.

The cases studied fell into two major groups: those with low, and those with high marrow eosinophil counts. Those with low counts (14 cases): 1 recovered spontaneously; 1 disappeared from observation without recovery; 6 were successfully splenectomized; 4 died (1 before, 1 during and 2 after splenectomy), and 2 were chronic. Those with high marrow eosinophil counts (16 cases): 12 recovered spontaneously; 4 were successfully splenectomized; and none died.

Analysis of Cases. Cases 1 to 9 and 28 to 30. *Characterized by high number of eosinophils in the marrow and spontaneous recovery.* It is believed that these cases are secondary to sensitivity to foods, drugs, or microörganisms, and that when the offending agent is removed, recovery ensues. It is most likely that the thrombocytopenia is precipitated in "allergic" individuals by the action of a trigger mechanism, and that the clinical symptoms represent a "summation" effect. Only on this basis can it be explained that these episodes are unique and do not recur even though many of the offending agents continue to exist in the patient's milieu. It is our impression that transfusions of blood hasten recovery. In acute cases, where bleeding is extensive, transfusions act by partially replacing platelets. For this reason it has been our custom to employ fresh in preference to stored blood. It is interesting that Case 5 should have had so slow a recovery. Two explanations for this are offered: (1) he was given pectin derived from apples and oranges, two of the fruits to which he was found highly "skin sensitive"; and (2) he was not placed on an elimination diet for several weeks. It is recognized that skin sensitivities do not necessarily reflect marrow sensitivity, so that even though the patient may be found "skin sensitive" to something, he is not necessarily "marrow sensitive," and by the same token negative skin sensitivity does not preclude marrow sensitivity. Much work remains to be done on this subject before it can be removed from the realm of speculation. The significant conclusion to be drawn from this group is that it represents one in which complete recovery may be anticipated relatively shortly without the necessity of performing a splenectomy.

Case 10. *Characterized by few eosinophils in the marrow and spontaneous recovery.* This case apparently belongs to the previously described group. We feel that failure to examine the marrow until the platelets had returned to normal accounts for the disappearance of the eosinophilia.

Cases 11 and 12. *Characterized by few eosinophils in the marrow and a chronic course.* These cases represent the non-allergic type of chronic cases which are candidates for surgery. Both are relatively benign, even though one has a 3 year and the other a 17 year history.

Case 13. *Characterized by many eosinophils in the marrow and a chronic course.* The eosinophils in this patient's marrow were just over the arbitrary borderline on one occasion, but a repeat marrow examination 3 years later definitely placed him with the following group.

Cases 14 to 18. *Characterized by few eosinophils in the marrow, and responding to splenectomy.* In this group, cases varied from the fulminant course observed in Case 15, to the chronic and relatively benign course seen in Case 14. It is felt that these, together with the others characterized by low eosinophils, represent the so-called "essential," "primary," or "idiopathic" thrombocytopenias which, provided there is no dearth of megakaryocytes, respond well to splenectomy.

Cases 19 to 21. *Characterized by numerous eosinophils in the marrow, and responding well to splenectomy.* Each of these cases was observed over a relatively long period of time, but no attempts were made to determine either the effect of elimination diets or the possible causes of sensitivity, the cases antedating the recognition of the significance of marrow eosinophilia. These cases

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TABLE 2.—SUMMARY OF OBSERVATIONS ON 30 CASES WITH THROMBOCYTOPENIC PURPURA

Case No.	Name	Age (yrs.)	Sex	Color	Length of illness when first seen	Suspected etiology	Course	Termination	Treatment	Eosinophils per 1000 marrow granulocytes	Remarks
1	K. F.	41	M	W	2 days	None	Acute	Rec. 13 days	Blood trans.	52	
2	S. C.	24	F	C	4 days	Drug given after tooth extraction	Acute	Rec. 9 days	Blood trans.	63, 98, 83	
3	G. Y.	6	F	W	3 days	Resp. infect.	Acute	Rec. 7 days	Blood trans.	53	
4	O. M.	64	F	W	8 days	Anacin	Acute	Rec. 13 days	...	94	
5	G. B.	5	M	W	13 days	Food and sulfonamide sensitivity	Subacute	Rec. 30 days	Blood trans.; elim. diet	136	Extensive allergic investigation; multiple food sensitivity
6	Z. G.	47	M	W	4 days	None	Acute	Rec. 12 days	Blood trans.	83	
7	B. L.	35	M	W	21 days	Food—molds; aspirin	Subacute	Rec.	Elim. diet	76	Extensive allergic investigation; multiple food and mold sensitivity
8	S. W.	12	F	C	1 day	None	Acute	Rec. 20 days	Blood trans.	56	
9	G. L.	42	F	W	10 days	Neoarsphenamine	Acute	Rec. 14 days	Blood trans.	50	
10	A. J.	16	M	C	5 days	Resp. infec.; aspirin; bromo-quinine	Acute	Rec. 19 days	Blood trans.	38*	Stormy course with severe epistaxes
11	F. A.	39	M	C	17 yrs.	None	Chronic	Unch.	...	33	
12	G. E.	9	F	W	4 wks.	None	Chronic	Impr.	Blood i.m.; snake venom	32	Platelets 105,000 3 yrs. later; no bleeding
13	G. J.	20	M	W	10 yrs.	None	Chronic	Unch.	...	54, 36	
14	B. L.	45	F	W	18 yrs.	None	Chronic	Rec.	Splenectomy	41	
15	Z. E.	13	F	W	5 days	None	Acute	Rec.	Splenectomy	43, 35, 35	
16	W. A.	57	F	W	3 yrs.	None	Chronic	Rec.	Splenectomy	52	
17	J. M.	39	F	W	7 yrs.	None	Chronic	Rec.	Splenectomy	33	
18	M. M.	30	F	W	6 mos.	None	Chronic	Rec.	Splenectomy	33	

12	G. E.	9	F	W	4 wks.	None	Chronic	Impr.	Blood i.m.; snake venom	32	Platelets 105,000 3 yrs. later; no bleeding
13	G. J.	20	M	W	10 yrs.	None	Chronic	Unch.	. . .	54, 36	
14	B. L.	45	F	W	18 yrs.	None	Chronic	Rec.	Splenectomy	41	
15	Z. E.	13	F	W	5 days	None	Acute	Rec.	Splenectomy	43, 35, 36	
16	W. A.	57	F	W	3 yrs.	None	Chronic	Rec.	Splenectomy	52	
17	J. M.	39	F	W	7 yrs.	None	Chronic	Rec.	Splenectomy	33	
18	M. M.	30	F	W	6 mos.	None	Chronic†	Rec.	Splenectomy	33	Purpura complicated; T.B. of kidneys; Raynaud's disease of hands
19	K. S.	20	M	W	1 yr.	None	Subacute	Rec.	Splenectomy	78	
20	B. V.	11	F	W	7 mos.	None	Chronic	Rec.	Splenectomy	59	
21	M. C.	20	F	W	1½ yrs.	None	Chronic	Rec.	Splenectomy	52, 53	
22	R. K.	16	F	W	1 mo.	None	Subacute	Rec.	Splenectomy	81	Spleen revealed Boeck's sarcoid —subsequently found in lungs
23	U. L.	17	M	C	16 days	None	Acute	Died	Splenectomy	26	Operative death
24	B. S.	32	F	W	4 yrs.	None	Chronic†	Died	Splenectomy	37	Splenectomy after diagnosis of cerebral hemorrhage
25	B. N.	22	F	W	8 mos.	None	Chronic†	Died	Blood trans.	44	Died of cerebral hemorrhage before splenectomy could be performed
26	P. C.	6½	M	W	5 wks.	Sulfapyridine ?	Chronic	Impr.	Blood trans.	23	Platelets never over 65,000 during 2 mos.; disappeared
27	M. D.	40	F	W	1½ yrs.	None	Chronic	Died	Splenectomy	35	No platelet rise after splenec.
28	W. S.	9	M	W	4 wks.	Food	Subacute	Rec.	Elim. diet	322	
29	R. J.	25	F	C	3–4 yrs.	Food	Chronic	Rec.	Elim. diet	73, 50	
30	L. T.	2½	M	W	5 days	Food	Subacute	Rec.	Elim. diet	133	

* Marrow obtained at time platelets were rising, 3 days before discharge from hospital.
† With acute exacerbation.

seem to indicate that even if the thrombopenia is on an allergic basis, the removal of the spleen can be beneficial. The mechanism of this action is unelucidated. Case 21 may not strictly belong to this group, resembling Case 13 in its closeness to borderline. It is possible, in view of the evidence here presented, that these cases may have been spared splenectomy by further studies.

Case 22. *Characterized by increased numbers of eosinophils in the marrow, and responding to splenectomy.* This case should, strictly speaking, be classified as "secondary" thrombocytopenia, since the spleen itself was involved by Boeck's sarcoid. What effect this had on the marrow is conjectural. Whether the marrow eosinophilia represented a sensitization and a consequent thrombopenia similar to those of the other allergic types, or whether the eosinophilia was part of the underlying disease process and the thrombopenia secondary to the hyperactivity of the diseased spleen, cannot be deduced from the study of a single case, but we are inclined to the latter view.

Cases 23 to 25 and 27. *Characterized by few marrow eosinophils, and the death of the patients.* These cases varied from the acute, fulminant course seen in Case 23, to the chronic course of Case 24. These cases resemble Cases 13 to 18, which were also characterized by low eosinophil counts, but responded well to splenectomy. It is significant that the only 4 deaths in our series occurred in cases with few eosinophils in the marrow. It is felt, in retrospect, that had the significance of the low eosinophils been understood and these patients splenectomized without much procrastination, at least Cases 24 and 25 might have been saved.

Case 26. *Characterized by paucity of eosinophils.* This patient was observed for about 2 months, during which period there was considerable clinical improvement, without the platelets ever rising over 65,000. At the time of this study, he could not be traced for follow-up purposes.

Discussion. Since Werlhof's description (1735)[17] of purpura, we have made steady progress in elucidating the nature and differential diagnosis of the disease. Donne (1842)[4] was supposed to have originally described platelets ("globulins") in the blood, while Denys (1887)[3] was the first to show that there was a reduction of the circulating platelets in Werlhof's purpura. This helped differentiate the vascular purpuras and scurvy from the thrombocytopenic forms. With the demonstration by Wright (1910)[18] that platelets arose from the megakaryocytes in the marrow, and the recognition that in spite of the blood thrombocytopenia the marrow megakaryocytes were present in normal or even increased numbers, either a megakaryocyte maturation defect (Frank, 1915)[5] or an increased platelet destruction (Kaznelson, 1916)[7] were suggested. Because of his belief in the destructive action of the spleen, Kaznelson was the first to have splenectomy performed in a case of thrombocytopenic purpura. The success of his case stimulated much interest, and within the next 20 years splenectomy became established as a curative procedure. As the number of cases increased, however, it became apparent that not all cases were cured by splenectomy. With the introduction of marrow biopsy by sternal puncture by Seyfarth (1923)[14] and its simplification by Arinkin (1929),[1] diagnosis could be made with more certainty since secondary purpuras could be ruled out.

In 1933 Denning[2] reported 3 cases of thrombocytopenic purpura following the administration of "Jotifixtabletten" (tablets containing 0.03% iodine), with 1 of the patients also developing thrombocytopenic purpura after Sedormid (allyl-isopropyl-acetyl-carbamide) ingestion.

Numerous reports confirming these findings have occurred since then, and other drugs (quinine, ergot, sulfonamides) have also been incriminated. In 1937 Squier and Madison[15] demonstrated that thrombocytopenic purpura could be produced by food allergy and cured by the removal of the offending agent. Thrombocytopenic purpura may also occur during or after infections, 12 of 153 cases being of this type in Rosenthal's[13] series.

Since presumably in allergic conditions the findings of an eosinophilia is common, and since the eosinophils have as their source the marrow, it might be expected that the marrow eosinophils be increased, even more markedly and more uniformly than those in the peripheral stream. Habelmann[6] has confirmed this by differential counts done on normal, moderately allergic, and severely allergic individuals.

To the present time the entire emphasis in marrow studies in thrombocytopenic purpura has been on the megakaryocytes. Limarzi and Schleicher[9] have summarized the present concept of the rôle of the megakaryocytes in thrombocytopenic purpura, emphasizing the inhibitory rather than the destructive effects of the spleen, a view with which we are not thoroughly in accord.

The eosinophils have been noted and commented upon in numerous publications dealing with thrombocytopenic purpura, but no previous correlation between their number and the clinical course has been made. Vogel, Erf and Rosenthal,[16] in commenting on the marrow findings in purpuras, note that "some of the cases showed a lymphocytosis and some of them had an eosinophilia. The cases of secondary purpura showed similar changes." Morrison and Samwick[10] note that "eosinophilia was also prominent in most of the cases. The latter was probably due to absorption of blood on the basis of foreign protein sensitization." Lawrence and Knutti[8] comment on the eosinophils in 5 of 6 of their cases. In 3 of them the eosinophils were increased, in 2 not increased. No attempt is made to draw conclusions or to correlate these findings.

When the correlation between high eosinophil counts and spontaneous remissions first became apparent to us, the findings were based on impressions only. In order to verify the impression we began determining eosinophil percentages, only to discover great discrepancies between what had appeared as obvious findings and actual counts. Interestingly, Nickerson and Sunderland[11] had apparently come to the same conclusion, for in their paper they state that "differential cell counts have shown no fundamental differences" between idiopathic thrombocytopenic purpuras, other purpuras, and normals. Reich and Kolb,[12] analyzing quantitative marrow studies statistically go so far as to state that "the validity of quantitative marrow determinations is very questionable."

Notwithstanding these objections, so obvious were the changes that we were convinced that some quantitative correlation could be established. It became obvious that one of the major causes of the great fluctuation in the percentage of eosinophils was the variability of the surrounding cell population. Thus, with bleeding there would be a

relative decrease in eosinophils due to increased erythropoiesis, while in children the greater number of lymphocytes tended to alter the percentage figures. Using comparative values rather than percentage figures (as discussed above), remarkably close correlation could be established between the height of the eosinophil level and the clinical course. Of the 30 cases studied, the correlation in 25 was perfect; 5 cases did not comply grossly. Of these, 1 had low eosinophils notwithstanding which he recovered spontaneously; 4 had to have their spleen removed, even though they had numerous eosinophils. Of these, 1 proved to be secondary thrombopenia on the basis of sarcoidosis of the spleen, while the other 3 may or may not have responded to conservative management, no allergic studies or treatment with this in mind being carried out. As was pointed out above, it is noteworthy that these cases recovered—even though their etiology may have been allergy—after removal of the spleen.

It is extremely significant that none of the 4 patients who died had an eosinophil count over 44, their counts being definitely below the arbitrary level. Attempts to correlate peripheral eosinophilia with marrow eosinophils or with clinical findings were unrewarded.

Multiple observations on the marrow were made in 5 cases. In Case 2 the eosinophils numbered 63 on admission, 98 two days later, and 83 four days after this. In Case 15 the eosinophils numbered 41 on admission, 35 three days later (the day of splenectomy), and 35 three days after this. In Case 13 the eosinophils numbered 54 on the first examination (slightly over borderline) but only 36 on repeat examination three years later. In Case 21 the eosinophils numbered 52 before and 53 one year after splenectomy. In Case 29 the eosinophils numbered 73 during the thrombocytopenic phase and 50 three months later when the patient had recovered. It would seem from these figures that the tendency for either a low or high eosinophil count is constant.

It is obvious that in dealing with marrow, which is influenced by so many variables and which reflects not only the stress and strain of the moment, but mirrors events both remote and recent, prognoses based on the numerical variation of a certain cell must be made with caution. It is our feeling, a feeling accentuated by the cases of exception, that the findings here reported do not represent either a fool-proof numerical prognostic system or a ready substitute for sound clinical judgment. Nonetheless, certain definite correlations are apparent, correlations which should add another tool to help make prognosis more certain and treatment more rational.

Summary and Conclusions. 1. Thirty cases of "primary" thrombocytopenic purpura are presented.

2. "Primary" thrombocytopenic purpuras may be divided into at last 2 types with respect to eosinophils: (*a*) with increased numbers of eosinophils in the marrow; (*b*) with no increase in marrow eosinophils.

3. Significant clinical, prognostic, and therapeutic differences are demonstrated between the two types.

4. It is suggested that the high eosinophilia is a manifestation of an

allergic state, of which the thrombopenia is merely another symptom, and therefore those cases having high eosinophil counts are thrombocytopenias *secondary* to sensitization, or "allergic" thrombopenias.

5. Cases characterized by high marrow eosinophils are thought to be due to sensitivity, are usually acute in onset and course, occasionally follow infections or the ingestion of drugs or allergenic foods, have relatively benign courses, and are followed by complete clinical and hematologic recovery.

6. In "allergic" thrombopenias, the elimination of the offending agent is curative; the removal of the spleen is *not* necessary; and blood transfusions seem to hasten recovery.

7. Thrombocytopenic purpuras with few eosinophils in the marrow remain in the "primary" group, and should have splenectomies.

8. No correlation was found between the eosinophils in the peripheral blood and the eosinophils in the marrow.

9. It is hoped that subsequent studies will further clarify the problem of "primary" thrombocytopenic purpuras and ultimately enable us to dispense with the term altogether in favor of etiologic diagnoses.

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INFECTIOUS MONONUCLEOSIS AND THE NEGRO

With a Report of 6 Cases

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Infectious mononucleosis as a disease entity has been known for over 50 years. The first record is that of Filatow[6] of Moscow, who de-

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scribed cases of acute enlargement of the cervical lymph glands without associated inflammatory changes in the mouth, nose or pharynx. Emil Pfeiffer[17] in 1889 gave an excellent description of the disease which he called "Drusenfieber" (glandular fever). In 1896, glandular fever first appeared in the American literature when West[20] described a comparatively large epidemic in eastern Ohio. The term "infectious mononucleosis" was introduced in 1920 by Sprunt and Evans,[19] who first emphasized the blood cytology. It was not until 1922 (37 years after the disease was first recognized) that the first case occurring in a Negro was reported by Longcope.[13] This patient was a boy who had an acute febrile disease with enlargement of the lymph nodes, spleen and liver. He also had a marked mononucleosis.

In 1940, Bernstein[2] published his excellent study of the disease based on a series of 65 patients at the Johns Hopkins Hospital. Not one of these was a Negro. He says in discussing these cases: "Sporadic cases, unless studied by the aid of repeated differential blood counts, may readily be overlooked while medical students or nurses, promptly admitted to the hospital for treatment of even a trifling illness, are almost certain to be correctly diagnosed by the routine methods of examination. This explanation, too, may account for the apparent paucity of cases observed in the dispensary and public wards as well as the rarity of infectious mononucleosis among Negroes, of whom not a single one appeared in our cases.[13] Indeed, but a single instance in a Negro has been noted in the literature." Wintrobe[21] in 1942 reiterates that the disease in the Negro is limited to 1 reported case (that of Longcope).

In April 1944, 22 years after the publication of Longcope's case, Johnson[9] reported 2 cases occurring in Negro children at the New Haven Hospital. These 2 cases are the first serologically proven cases in the Negro to be published. The first had a heterophil agglutination titer of 1:640. After adsorption with guinea-pig kidney the titer was 1:320. The second had a titer of 1:2560. Johnson states that "no explanation can be offered for the apparent rarity of the disease on a racial basis."

Anthropologic Considerations. Infectious mononucleosis occurs in many racial and ethnic types and it has been reported in many widespread areas throughout the world. America, Australia, France, Germany, Russia, and Great Britain have all had epidemic and sporadic cases. Benson[1] has written of the disease in Scotland. It has been seen in South America[8] and the Philippines. It was reported in Hong Kong in 1897.[3] Priest[18] has recognized it in Egypt. Infectious mononucleosis has been encountered in Trinidad[4] and in the Falkland Islands.[15] In Japan, the following epidemic fevers have been shown by the use of Paul-Bunnell tests to be identical with infectious mononucleosis:[11] tosa-netsu, tokushima-netsu and kagami-netsu. Bernstein is of the opinion that the disease has no racial preference. He mentions the epidemic followed at the London Hospital and reported by Gooding,[7] in which "20 of 27 cases occurred among Jews, a fact perhaps ascribable to the area served by the hospital."

Thus, it may be seen that, so far as is known, the occurrence of infectious mononucleosis does not appear to be limited by factors of geography or race; indeed, it is world-wide in its distribution, affecting many ethnologic varieties of man.

Furthermore, it can be seen why sporadic cases in the Negro would not come to the attention of physicians as readily as similar cases in others, especially in college infirmaries and elsewhere where either white patients predominate or have access to better diagnostic facilities.

There is then no known reason why the disease should not afflict Negroes as commonly, relatively, as the members of other races, and it does so in our series of cases.

Clinical Study. The occurrence of this disease in 6 Negroes in our series of 20 sporadic cases at the Receiving Hospital from 1934 to 1944 indicates that the disease is not as rare in the Negro as has been heretofore supposed. The case reports to be presented represent 30% of our total cases in a hospital where only 25% (as determined by spot samplings of several recent years) of the population is composed of Negroes.

The first 4 cases had heterophil agglutination titers of 1:224 or above. The fifth had a titer of 1:160 which is accepted as positive by Bernstein and others. The last case was seronegative although his titer could be classed as "borderline" as defined by Davidsohn[5] (*i. e.*, 1:56 to 1:112). He had, however, positive clinical and hematologic evidence for the diagnosis. In addition, 2 patients, each with a titer of 1:112, are mentioned.

Case Reports. CASE 1. F. M., an 18 year old Negro male, was admitted on August 8, 1941, complaining of a severe sore throat, malaise, and fever of 1 week's duration. On the first day of his illness his eyelids were swollen. On the day prior to admission the patient experienced a chill. There was no cough. The past history included attacks of mumps, pertussis, measles and chickenpox. At the age of 9 a tonsillectomy and adenoidectomy was done. Physical examination revealed a well-developed and well-nourished male who appeared acutely ill. Temperature 104.2°, pulse 82, respiration 20. The oral and nasal mucosa, the soft palate and uvula were markedly edematous and injected. There was a thick, greenish, purulent postnasal discharge. There were bilateral tender enlarged anterior and posterior cervical, submental, submaxillary and pre-auricular glands. The inguinal glands were small and shotty. On August 11, the spleen was palpated 2 fingerbreadths below the left costal margin.

Laboratory Data. Roentgen rays of the sinuses showed a slight cloudiness of the ethmoids and frontal sinuses. The urine was negative. A Kline test was negative and throat cultures were negative for diphtheria. Examination of the blood revealed a leukocytosis of 18,400 with 67% lymphocytes. The hemoglobin was 13 gm.

On August 13 the following blood study was made (E. C. V.): Red cells 5,120,000, reticulocytes 0.4%, hemoglobin 87%, thrombocytes 123,000, white cells 15,500 (neutrophils [stab] 12% and [segmented] 15%, lymphocytes 67%, monocytes 6%). There were many bizarre large lymphoid cells like those seen in infectious mononucleosis.

The heterophil agglutination on August 14 (2 weeks after onset of illness) was positive through dilutions of 1:1026. The patient was given sulfathiazol and local therapy and was discharged on August 15, after the temperature had been normal for 3 days.

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CASE 2. M. G., a 13 year old Negro girl, was admitted to the Receiving Hospital on Sept. 25, 1943, complaining of a sore throat of 24 hours duration. She had had frequent sore throats and colds during the past 12 months. Physical examination revealed a well-developed and well-nourished girl in no acute distress. Temperature 102.8°, pulse 110, respiration 20. The nasal turbinates were swollen and injected as were the tonsils. Both the anterior and posterior cervical nodes were enlarged and tender. There were shotty inguinal nodes and palpable nodes in the left axilla. The liver and spleen were not palpable. The admission diagnosis was acute tonsillitis.

Laboratory Data. The urine was negative on several examinations. Nose and throat cultures were negative for diphtheria. The Kahn test was negative. Blood studies revealed: hemoglobin 10.5 gm., leukocytes 19,500 (of which 36% were "abnormal and toxic" lymphocytes), neutrophils 51% (35% were filamented and of the non-filamented forms—5 myelocytes, 5 stab cells and 6 juvenile forms). There were 5 monocytes, 2 blast cells, 2 basophils and 4 eosinophils, and the smears were reported as "suggestive of infectious mononucleosis." The heterophil agglutination was positive on September 29 (6 days after onset of symptoms) in a titer of 1:3594. This is the highest titer ever observed at this hospital. On September 30 the leukocyte count was 11,900, band form neutrophils 9%, polymorphonuclear neutrophils 20%, atypical lymphocytes 22%, eosinophils 1%, monocytes 3%. "The erythrocytes appear normocytic and normochromic. The majority of the atypical lymphocytes are reticular (Type 1 of Downey). Impression: infectious mononucleosis." (Dr. Lawrence Berman, Hematology Laboratory.)

On October 1 a tonsillectomy and adenoidectomy was done and the patient was discharged on the next day. She received sulfathiazol while in the hospital.

CASE 3. M. P., a 27 year old married female Negro, was admitted on Nov. 27, 1943, with a diagnosis of possible acute appendicitis. Her past history revealed that she had had a course of sterile milk shots at the Gynecologic Clinic of this hospital 1 year previously for chronic pelvic inflammatory disease. She had been married 5 years during which time she had been troubled by a chronic vaginal discharge. She had had 3 spontaneous miscarriages, the last occurring 4 months prior to admission. Two to 3 weeks before coming to the hospital she had a "head cold" associated with chills, sweating, cough, chest pain and a small amount of blood-streaked sputum. One week prior to admission she noted a mid-abdominal pain of sudden onset associated with nausea, vomiting and constipation. Physical examination revealed a well-developed and well-nourished, but markedly dehydrated woman in moderate distress. Temperature 99, pulse 70, respiration 22. The throat was injected, the tonsils had been removed, and a bleeding point was noted in the right nostril. No lymphadenopathy was noted. The spleen was not palpable but the liver was felt 4 fingerbreadths below the right costal margin. The liver was tender and the abdominal tenderness was mainly in the right upper quadrant. There was bilateral costovertebral angle tenderness and there was a dermatitis later diagnosed as of contact etiology. The pelvic examination was deferred because she was menstruating but when done revealed an acute exacerbation of her pelvic inflammatory disease.

Laboratory Data on Admission. There was a leukocytosis of 14,850 (monocytes 20%, neutrophils 66%, lymphocytes 13%). A recheck the same day showed leukocytes 13,100 (monocytes 14%, neutrophils 76%, lymphocytes 8%). It is very likely that the monocytes were in reality atypical lymphocytes. There was no anemia or jaundice. The bleeding time was 1 minute 45 seconds and the clotting time was 2 minutes. The Kline test was negative, the blood urea was 153 mg. The urine contained 100 white cells, 1+ albumin and trichomonads. The albumin-globulin ratio was normal. Urine cultures were positive for *Staphylococcus albus*, *B. coli* and, later, a non-hemolytic streptococcus. By December 6 the blood urea had fallen to normal levels where it remained.

On December 7 the submandibular and submaxillary glands were enlarged

and tender. The liver was still palpable but the spleen was not. The following day (24 to 31 days after onset of symptoms) the heterophil agglutination was positive in dilutions through 1:224. Chest Roentgen rays, retrograde and intravenous pyelography and urea clearance tests all yielded normal results. The blood picture on December 6 was as follows: leukocytes 11,100, neutrophils 63% (filamented 60%, non-filamented 3%), lymphocytes 20%, monocytes 13%, 1 plasma cell, 1 basophil and 20% eosinophils.

The patient was treated with sulfathiazol, vitamins and sedation. Fluids were forced. Her temperature ran a septic course until December 14 (3 weeks after admission). At this time her liver was no longer palpable and her symptoms had disappeared. Final diagnosis: acute exacerbation of chronic pelvic inflammatory disease, bilateral acute pyelonephritis and infectious mononucleosis.

This case reëmphasizes the fact that infectious mononucleosis is not only very protean in its manifestations but may well be associated with or obscured by coëxisting disease.

CASE 4. M. M., a 27 year old Negro female, was admitted to the hospital on Jan. 7, 1944. She had been well until the 1st week in November 1943, since which time she had suffered from "a chronic cold" associated with a non-productive cough. One week prior to admission she developed a productive cough and a pain in the left lower costal region, anteriorly, for which she was given a sulfonamide drug by her family physician. Two days prior to admission she had blood-streaked sputum, fever, nausea and vomiting.

The physical examination on admission was essentially negative except for tenderness at the left costal margin anteriorly. There was no lymphadenopathy or splenomegaly. Temperature 98, pulse 110, respiration 24.

Laboratory Data. Roentgen rays were negative for rib fracture and showed slight exaggeration of the bronchovascular markings throughout both lung fields. It was the impression of the radiologist that these findings were consistent with "influenza with left pleuritis or recurrent bronchitis." The urine was negative. The white count was 9500 (lymphocytes 54%, neutrophils 42%, 2 monocytes and 2 eosinophils). The Kahn and a blood culture were negative. On January 11 the urine contained 5 to 10 white cells and a urine culture was positive for non-hemolytic streptococcus, *Staphylococcus albus* and diphtheroids. The following day the white count was 5850 (lymphocytes 46%, neutrophils 49%, monocytes 3%, 1 basophil and 1 eosinophil).

On January 14 (2 weeks after onset of acute symptoms) the heterophil agglutination was positive through a dilution of 1:224. The patient remained in the hospital for 1 week and was symptomless after the 2nd day except for tenderness along the left costal margin and over the spleen which was never palpable. No lymphadenopathy was ever noted in this case.

CASE 5. D. D., a 6 year old Negro boy, was admitted on Feb. 21, 1942, with a diagnosis of acute tonsillitis and possible blood dyscrasia. He had had a sore throat and a fever for several days with swelling of the glands of the neck. He had had a tooth extracted 4 days prior to admission and had bled for 2 days thereafter. He had a nosebleed on the morning of admission. He had been immunized against diphtheria and had had pertussis and measles. Physical examination revealed a well-developed and well-nourished but acutely ill boy. Temperature 103.2°, pulse 140, respiration 20. The tonsils were enlarged and inflamed with follicular surfaces. There were large tender submaxillary glands on the right and smaller ones on the left side. There was bilateral tender shotty cervical adenopathy. The spleen and liver were not palpable.

Laboratory Data. The urine was negative. Nose and throat cultures were negative for diphtheria. Examination of the blood revealed a leukocytosis of 12,550 (neutrophils 78%, lymphocytes 22%). The hemoglobin was 8 gm., the red cells 3,420,000.

He was placed immediately on sulfathiazol, cod-liver oil, orange juice and

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iron. An ice collar was employed for local relief. The following day his temperature had dropped almost to normal and thereafter ranged between 98° and 99.5° until March 1 when it spiked to 101° (the sulfathiazol was discontinued on February 27). On March 5 the spleen became palpable 2 cm. below the costal margin. On this day the patient was started on sulfadiazine and the temperature returned to normal where it remained. The heterophil agglutination on March 10 was positive in dilutions through 1:128 and on March 19 through a dilution of 1:160 (over 1 month after onset of symptoms). The Kahn test, tuberculin test and chest Roentgen rays were negative as was a wet preparation of blood for sickle cells. The blood examinations are charted below:

Date	Hb.	R.B.C.	W.B.C.	Neut.	Lympho.	Eosin.
2/22/42 . . .	8.0	3,420,000	12,550	78	22	
2/27/42 . . .	8.5	3,340,000	9,900	87	13	
3/9/42 . . .	9.0	4,450,000	9,700	48	52	
3/14/42 . . .	9.0	..	11,300	62	35	3

By March 19 all the enlarged lymph nodes had decreased in size and the spleen was no longer palpable. On March 24 the patient was discharged.

It will be noted that although this patient's heterophil agglutination titer was only 1:160, he had lymphadenopathy, an enlarged spleen, sore throat and, at one time, a lymphocytosis.

Case 6 was interesting not only in that he was a Negro but also seronegative and his infectious mononucleosis was associated with acute thrombocytopenic purpura. This complication is exceedingly rare, there being only a very few unimpeachable cases in the literature. Magner and Brooks,[14] and Lloyd[12] have each reported a case in which first of all the diagnosis of infectious mononucleosis was unequivocal (their patients having positive Paul-Bunnell tests, lymphocytosis, typical blood cytology and lymphadenopathy, and the former splenomegaly as well). In addition, both cases had bleeding, purpuric eruptions, prolonged bleeding times, and reductions in platelet counts. Lloyd's case had a sternal puncture which showed no abnormality of the various bone marrow elements. Sternal puncture in our case also showed no abnormality.

Hemorrhagic skin eruptions, epistaxis, hematuria or bleeding from other mucous membranes (as in Case 5) in the presence of a normal platelet count is not uncommon in infectious mononucleosis and is probably due to capillary damage.

Case 6. J. H., a 13 year old Negro boy, was admitted to the Nose and Throat service on Sept. 15, 1940, complaining of a severe sore throat of 3 days duration. He had such marked cervical lymphadenopathy that his whole neck appeared to be swollen. His past history was negative except for an attack of mumps. He was in good health until September 8, at which time he became conscious while sitting in a theater that his neck glands were enlarged. There was associated pain and swelling of the eyelids and a mild headache. Four days later the adenopathy and other symptoms subsided and he felt improved. On September 15 the swelling in the cervical nodes returned and he entered the hospital.

Physical examination showed a well-developed and well-nourished youth appearing acutely ill. Temperature 103°, pulse 80, respiration 18. The tonsils were hypertrophied but not injected. There were several petechiæ on the soft palate. The anterior cervical, submaxillary and submental lymph nodes were enlarged, tender and firm to palpation and seemed to be matted.

The axillary glands were enlarged and tender. The spleen was palpable 2 fingerbreadths below the costal margin.

The impression was that he had infectious mononucleosis and he was transferred to the medical service as soon as the following blood study was reported: Hb 12.5%, white cells 20,000 (lymphocytes 80%, monocytes 5%), neutrophils 15%. The urine was negative. A Kahn test was negative and throat and nose cultures were negative for diphtheria. On the following day a complete blood study was made by one of us (E. C. V.) and is recorded below:

Hb	84%
R.B.C.	4,180,000
W.B.C.*	23,000
Reticulocytes	1.5%
Platelets	204,000

* 5% stab forms, 3% segmented, 1% eosinophil, 1% basophil, 84% lymphocytes, 6% monocytes.

"Slight normochromic anemia. Leukocytosis with neutropenia and an absolute and relative lymphocytosis. Lymphocytes are the type seen in benign infectious mononucleosis. Impression: infectious mononucleosis."

The patient was treated with sedation and an ice collar for local relief. On September 25 the heterophil agglutination was positive through a titer of 1:64 (over 2 weeks after onset of symptoms). On this day the patient developed a severe nosebleed and had a prolonged prothrombin time (17 seconds, the normal being 12 seconds by Quick's method). He developed purpuric spots on both thighs and on October 1 the Rumple-Leede test was markedly positive. It remained so for some time. Following the epistaxis the platelets fell to 20,000. A diagnosis of acute thrombocytopenic purpura was made. The bone marrow on study (E. C. V.) had a normal appearance with many normal megakaryocytes present. The prothrombin time remained elevated and the platelet count remained depressed until after discharge. On October 2 the Paul-Bunnell test was positive in dilutions through 1:16 only. On October 21 the hemoglobin was 81% and red blood cells 4,400,000. The white blood count was 7400 (lymphocytes 51%, neutrophils 39% [28% filamented and 10 non-filamented, 1 juvenile]). The platelets were 36,000. On October 22 a bromsulphonphthalein test showed no retention of dye at the end of 30 or 60 minutes. The patient was discharged on October 23. The final diagnosis was infectious mononucleosis and acute thrombocytopenic purpura.

Although we regard a titer of 1:64 as negative, we feel that the diagnosis is well established on clinical and hematologic evidence. It might be well to point out that well-substantiated seronegative cases such as that of Pearman and Brumm[16] do occur. They state in their report that "at present there is a certain number of seronegative cases in almost every large series reported, chiefly in sporadic cases among children." Their patient had a titer of 1:10. Also, there are 5 seronegative cases in Bernstein's series of 65. Bernstein states that "if the clinical picture is sufficiently characteristic therefore, a negative Paul-Bunnell test does not preclude the diagnosis of infectious mononucleosis any more than a negative Wassermann reaction rules out syphilis."

In addition there have been 2 Negroes who developed titers of 1:110 while in the hospital. Both had generalized lymphadenopathy. Neither had a palpable spleen. One had lymphocytosis. The first, a 21 year old woman, had given birth to her third baby 2 weeks prior to admission. She had a pyelonephritis and a septic fever. The second,

a 17 year old boy, was markedly jaundiced; he had an acute hepatitis with a persistently positive serology. Both probably had infectious mononucleosis.[10] Unfortunately, neither had differential absorption tests or complete hemograms so the diagnosis could not be positive. None of the cases reported here gave any history of having received serum.

Since this article was submitted for publication Ray and Cecil[18a] have reported 3 serologically proved cases of infectious mononucleosis in negroes at the Medical College of Virginia Hospitals. One of these cases was complicated by sickle cell anemia. They also point out that 4 of the 21 cases reported by Werlin, Dolgopol and Stern from the Willard Parker Hospital in 1941 were negroes. Only one was given in detail, and in this the heterophil antibody titer was positive 1:112 (after absorption, 1:56). On admission the white count was 27,800 with 57% lymphocytes. On the 8th day there were 17,000 white cells with 54% lymphocytes of which 13% were abnormal. These 7 cases bring the correct total of reported cases in the Negro to 16.

Summary. Infectious mononucleosis although recognized as a disease entity for over 50 years has been reported in only 3 Negroes. Two of these, having been reported subsequent to the development of the Paul-Bunnell test (1932), are confirmed serologically.

The 6 cases reported here represent 30% of a series of 20 cases which have been diagnosed at the Receiving Hospital during the past 10 years. The proportion of Negro patients in this hospital is 25%. Inasmuch as these cases were all sporadic rather than epidemic there is an indication that the disease is as common as in the whites at this hospital.

Two of the cases had heterophil agglutination titers over 1:1000; 2 of the cases were positive in titers through 1:224; 1 was positive in titers through 1:160; and 1 was seronegative (1:64). This last case had excellent clinical and hematologic evidence for the diagnosis. He also had a rare complication, acute thrombocytopenic purpura. Two other probable cases of infectious mononucleosis are mentioned.

Conclusions. 1. Six cases of infectious mononucleosis in Negroes are reported. Five of these are serologically confirmed. One case was seronegative.

2. The seronegative case had an associated acute thrombocytopenic purpura, which is a rare complication. The 2 best substantiated cases of this complication reported in the literature are cited.

3. In addition 2 probable cases are mentioned but are not included in the series.

4. These cases bring the total of reported cases in Negroes to 9 and the total of serologically, proved cases to 7.

5. Infectious mononucleosis at this hospital is relatively as common in the Negro as in the white.

6. The widespread belief that infectious mononucleosis is rare in the Negro appears to be no longer tenable.

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SPONTANEOUS PNEUMOTHORAX AS A COMPLICATION OF PNEUMONIA IN ADULTS*

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Pulmonary tuberculosis is commonly thought to stand first as an exciting cause of spontaneous pneumothorax. It has been variously estimated that tuberculosis accounts for from 70%[6] to "at least" 80 or 90%[14] of all cases. The less common causes of spontaneous pneumothorax are abscess or gangrene of the lung, bronchiectasis, septic infarct, rupture of an emphysematous vesicle, rupture of a cyst in a congenital cystic lung and gas-producing organisms in a pleural effusion. It is also known to occur in healthy individuals without any clinically demonstrable evidence of pulmonary disease. In the group of extrapulmonary causes are perforation of the esophagus, rupture of a gastric ulcer or carcinoma through the diaphragm, and rupture of a liver abscess.

From the perusal of literature and text-books on general medicine, it appears that spontaneous pneumothorax as a complication of lobar or bronchopneumonia has escaped general recognition and has not come to constitute a part of common knowledge. While not an unusual complication of pneumonia in children,[4,7] it is still considered

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as an unusual occurrence in the course of pneumonia in adults. According to Lord[12] "Pneumonia is to be regarded as a cause only, insofar as it leads to conditions to which pneumothorax may be secondary." Of these conditions, perforation of empyema into the lung or rupture of an area of pulmonary abscess or gangrene into the pleura are mentioned. In Tice's "Practice of Medicine"[16] pneumothorax in association with pneumonia is considered to be "a very rare occurrence and has been noted most often when empyema has ruptured into a bronchus." In other words then, not pneumonia *per se*, but rather such pathologic processes as abscess, gangrene or empyema are credited with production of spontaneous pneumothorax. However, there have been reported in literature a few cases of pneumothorax in association with pneumonia not complicated by any of the sequelæ above mentioned. To these I add 2 more cases recently observed. Although there have been very few such cases reported, and in spite of statements made by some[8] that "the association of pneumothorax with pneumonia is extremely rare," it would appear that this condition is more frequent than has heretofore been thought.

Review of Literature. The earliest reference in literature to occurrence of spontaneous pneumothorax in association with pneumonia that I have been able to find is a report by Von Mering,[18] who in 1886 recorded 2 such occurrences in a review of 422 cases of pneumonia, an incidence of 0.47%. The diagnosis had apparently been made on the basis of physical findings only. The next report is by Aldridge and Mooring[1] who in 1915 described a case of pneumothorax following pneumonia in a bricklayer, age 40. The patient made an otherwise uneventful recovery. The same authors quote a personal communication from Dr. Arthur Latham as follows: "Some few years ago the pneumonia cases at the London General Hospital were analyzed for a period of 10 years in the Medical Section of the Royal Society of Medicine. As far as I know, in over 7000 cases there were not more than 3 complicated by pneumothorax, and 2 of them proved fatal."

During the influenza epidemic of 1918–1919, Berkley and Coffen[5] reviewed 1701 cases of bronchopneumonia, in which series 9 cases developed extensive subcutaneous and interstitial emphysema. Of these 9 cases, 2 had an associated spontaneous pneumothorax. The authors stated that it has been impossible to establish any relationship between the casual organism in a case of pneumonia and development of emphysema or pneumothorax. The organisms found were pneumococcus, non-hemolytic streptococcus, and *H. influenzæ*. However, in 1 of these 2 cases with spontaneous pneumothorax, in addition to Type IV pneumococcus, acid-fast organisms were also discovered in the sputum. A tuberculous origin of spontaneous pneumothorax thus remains in question in this particular patient. It was thought that violent coughing served as an inciting factor, leading to the rupture of the lung. The report of Berkley and Coffen apparently served as a basis for the statement to be encountered in Tice's "Practice of Medicine"[16] to the effect that in the bronchopneumonia during the influenza epidemic of 1918–1919, coughing in some cases was so severe

"that it led to rupture of the lung. In four-fifths of these cases, however, it led to interstitial and, therefore, often to subcutaneous emphysema; only in one-fifth of them did pneumothorax develop."

Bassel,[3] reviewing 23 consecutive cases of spontaneous pneumothorax, refers to 3 found to be the result of pneumonia. Glickman and Schlomovitz[10] cite 2 cases of spontaneous pneumothorax following bronchopneumonia out of 82 cases of spontaneous pneumothorax following different conditions, an incidence of 2.5%. However, direct reference to the source[9] quoted by these authors surprisingly fails to reveal such actual occurrence. Therefore, these 2 cases have to be discounted.

Minet and Houcke[13] encountered 2 cases of pneumonia, 1 pneumococcal, complicated by small pneumothorax. Both patients recovered. Another case with bronchopneumonia complicated by pneumothorax with serous effusion died. At autopsy there was no evidence of acid-fast infection.

Aubertin, Lereboullet and Pergola[2] reported 2 cases. One with pneumonia was complicated by a pneumothorax which evolved into a pyopneumothorax with death of the patient. On autopsy a purulent effusion in the left pleural cavity, consolidation of the left base with diffuse changes of bronchopneumonia in the rest of the lung and a small cortical abscess posteriorly "without any apparent rupture into the pleura" were found. There were no acid-fast organisms found. In another patient pneumothorax was not accompanied by effusion and he successfully recovered.

Thomas[17] reported 7 cases of pneumonia complicated by pneumothorax. The recovered organisms were pneumococcus and non-hemolytic streptococcus. In 1 patient there was an associated serous effusion, in 2 empyema, and in the remaining 4 only pneumothorax. In 1 case initially a serous effusion later became purulent In another case there developed an abscess of the chest wall. All 7 patients recovered.

Hyde and Hyde[11] found "a small apical spontaneous pneumothorax on the affected side" as a complication in 2 out of a series of 51 cases of primary Friedländer pneumonia.

Report of Cases. Case 1. F. S., a 43 year old man, was admitted to the hospital on May 7, 1943, with complaints of chest pain, fever and cough of 3 days duration. He had been in excellent health in the past. On entry he was seen to be well developed and well nourished and appeared to be acutely ill, with rapid respirations and a pulse of 108. There were signs of consolidation of the right lower lobe confirmed by Roentgen ray studies. There were no other remarkable physical findings. There was a leukocytosis of 15,200. Pneumococci, Type VII, were found in the sputum. The response to therapy with sulfonamides was satisfactory, and the recovery was clinically uneventful. However, a routine check Roentgen ray film of the chest taken on May 14 revealed the presence of a small apical pneumothorax. Repeated examinations of concentrated sputum specimens failed to reveal any acid-fast organisms. No tubercle bacilli were found on cultures and the guinea-pig inoculation with the specimen of sputum also failed to show a tuberculous infection. On resorption of pneumothorax, there were no demonstrable lesions in the lung fields by Roentgen ray.

Case 2. R. L., a 49 year old white male, was first admitted to the hospital in November 1938 for treatment of traumatic compression fracture of the

XUM

first and second lumbar vertebræ. The second admission was on Dec. 22, 1943, at which time he complained of fever, cough and weakness with breathlessness of 1 week's duration. The night before entry into the hospital he was seen by the family physician who made a diagnosis of pneumonia and recommended hospitalization. He had the usual childhood diseases but no other illness. He had been in good health all his life.

On physical examination the patient was seen to be a well-developed, fairly well-nourished man of about the stated age, acutely ill, cyanotic, with rapid and shallow respirations and a rapid, feeble, irregular pulse, 120. The temperature was 102° F. The blood pressure was 110/60. The examination of the heart did not reveal any significant findings, except for rather frequent premature beats. There was impairment of resonance on percussion with râles over the entire lung field on the right. There were no other significant findings.

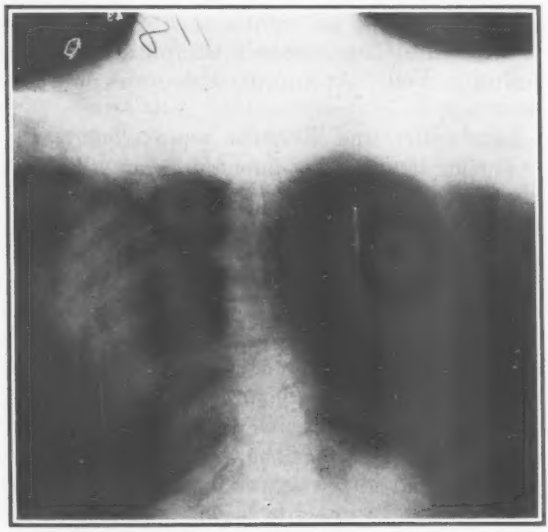

FIG. 1.—Case 2. Diffuse opacity in right lung.

The urinalysis revealed the presence of 2+ albumin and some hyaline casts with a few granular casts. Red blood count was 3.7 million per c.mm.; hemoglobin, 9.5 gm. Total leukocyte count was 7200 (89% neutrophils). Serologic blood tests were negative. Neufeld typing tests for pneumococci in the sputum (Types 1 to 33 inclusive) gave negative results. Roentgen ray film of the chest taken bedside revealed diffuse opacity in the right lung field (Fig. 1). Blood culture taken on admission failed to show any bacterial growth.

Within 1 hour after entry the patient became semistuporous. Because of the critical condition of the patient, sulfadiazine was administered intravenously, 4.5 gm. of the sodium salt as a 5% solution in sterile water. It was thought that frequent extrasystoles could be interpreted as indicative of an underlying organic heart disease with the heart laboring under the stress of an overwhelming infection. At any rate, digitalization was considered advisable. Six cc. of cedilanide (3 mg.) were given intravenously in addition to sulfadiazine and the patient was put into an oxygen tent. The following morning he seemed to have improved; he was conscious, well oriented, but still toxic. Blood sulfadiazine concentration of 12.6 mg. per 100 cc. of the free drug was reported. The patient was started on sulfadiazine orally, 1 gm. every 4 hours, and was also given another 2 cc. of cedilanide intravenously followed by cedilanide by mouth, 1 tablet 3 times a day. The following (2nd) day extrasystoles were no

longer present. On the 5th hospital day the temperature gradually dropped to 99° F. and the patient's condition seemed to be satisfactory.

However, this improvement was not lasting, as the temperature began to rise again in a few days and reached 103.6° F. on the 10th day. Examination of the lungs at that time revealed hyperresonance with absence of breath sounds over the entire right lung field, except for the base where the percussion note was dull, but the breath sounds absent. This suggested a hydro- or pyopneumothorax and the Roentgen ray film of the chest confirmed this suspicion. It showed a pneumothorax on the right with approximately 30% compression of the lung and a fluid level in the pleural cavity at the level of the seventh rib posteriorly; the left lung field was clear (Fig. 2). Thoracocentesis revealed the presence of a small amount of straw-colored fluid. The patient continued to run a septic course with rapidly progressing general failure. His temperature went up to 105° F. Thoracocentesis was repeated and again yielded clear fluid. No organisms were found in both specimens of pleural effusion on smear or culture and later the guinea-pig inoculation tests were reported as negative

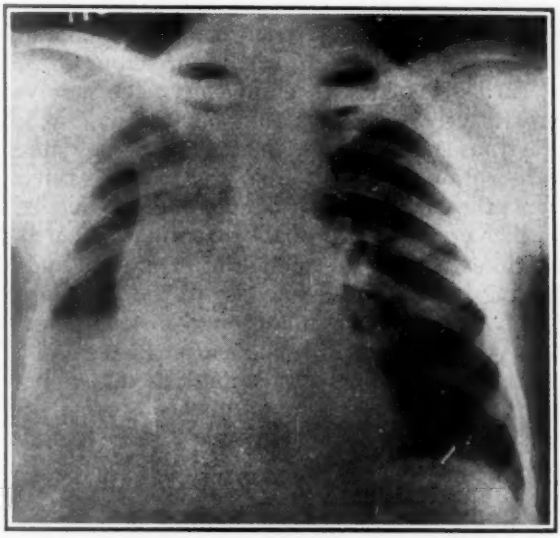

FIG. 2.—Case 2. Right pneumothorax and fluid.

on the same specimen. No tumor cells were seen in the centrifuged sample. Sputum was repeatedly negative for acid-fast organisms and tuberculin injected intracutaneously did not give a positive reaction. Another blood culture taken on January 6 failed to reveal any growth. On the same day the total leukocyte count was found to have mounted to 17,200 (94% neutrophils) with marked "shift to the left."

The patient expired on Jan. 12, 1944, 22 days after admission.

Autopsy. The *pleural cavities* contained no excess of free fluid. The right *lung* was found to be partially collapsed and adherent along its posterior surface to the chest wall by moderately dense fibrous adhesions. The lung weighed 500 gm., with dull and granular surfaces covered with fibrin, and presented the usual appearance of bronchopneumonia. The bronchial mucosa was congested and the bronchi were partially filled with purulent exudate. The pulmonary vessels were patent. The *heart* weighed 300 gm., and on dissecting the organ a soft, friable, reddish-brown, smooth-surfaced vegetation, varying from 4 to 6 mm. across, could be seen in midportion of each cusp of the aortic valve along the line of closure; these were firmly attached to the valve. A

similar vegetation, measuring 6 mm. in its greatest diameter, was found along the line of closure of the aortic cusp of the mitral valve.

Anatomic Diagnoses. (1) Pneumonia, bronchial, unresolved; (2) pleuritis, acute; (3) pneumothorax; (4) endocarditis, acute, bacterial.

Discussion. In the 2 cases presently reported spontaneous pneumothorax occurred as a complication of pneumonia, in 1 instance being accompanied by sterile pleural effusion. In 1 of these cases the possibility of tuberculosis as an underlying process responsible for this occurrence was rather definitely ruled out by repeated studies of the sputum by smear, culture and guinea-pig inoculation, as well as the subsequent clinical course with serial Roentgen ray studies. In the other case the autopsy findings conclusively eliminated the presence of a Koch's infection.

From the review of the scant literature on the subject, along with the study of the cases here reported, it appears that spontaneous pneumothorax occurring in association with pneumonia may be classified into two varieties: (1) with or without serous effusion, presumably sterile; (2) associated with empyema. The first variety represents a comparatively innocuous complication, not in itself fraught with any disastrous consequences, and usually ending in recovery with uneventful absorption of the air from the pleural cavity. It apparently represents the closed type of pneumothorax; that is, the pulmonary fistula which creates it is probably of a small caliber and as a result it very often closes with the retraction of expiration and opens again in the succeeding inspiration, giving rise to the valvular effect. The etiology of this variety of pneumothorax is debatable. At least a partial clue may be found in the explanation Pierce and Dirkse[15] give for the formation of pulmonary pneumatocele and pulmonary cysts. These authors believe that a certain sequence of events in the course of an antecedent pulmonary infection offers a more logical explanation for the origin of multiple cystic disease of the lungs than congenital abnormalities. They maintain that since necrosis of the bronchiolar walls associated with small abscesses arising in these structures is a relatively frequent occurrence in the course of a bronchopneumonia, the rupture of alveolar or bronchiolar walls with the production of an interstitial emphysema may occur. This would afford opportunity for air to dissect along the septa during cough, with the formation of subpleural blebs. "With the bronchial infection there is an interstitial inflammation, as contrasted with the intra-alveolar infection of the lobar type. Peribronchial alveoli become involved. The peripheral alveoli may be affected secondary to the changes in bronchi and bronchioles, or obstructed by the exudate in the latter. The tendency to confluence of involved lobular areas is common, often with acutely emphysematous intervening lobules due to partial obstruction of the proximal bronchus or bronchiole by exudate and inflammation. There is then, in association with bronchopneumonia, a ready opportunity, depending upon the dominant lesion, for the development of: (*a*) a saccular to cystic bronchiectasis by means of the damage to the bronchiole and bronchiolar walls; or (*b*) focal acute lobular vesicular emphysema

which may not be relieved because of incomplete resolution in or repair of the proximal airway; or (*c*) peripheral bullous (subpleural) emphysema by means of the rupture of the bronchial walls which permit an escape of air into the interstices . . . . The term pneumatocele properly denotes the tumorous nature of the air-filled dilated or ectatic alveoli or lobular spaces, corresponding to singular or multilocular character assumed respectively by the emphysematous air spaces. Our concept of the origin of the pneumatocele is the acute lobular emphysema associated with lobular pneumonia. A persistent check-valve obstruction of the bronchial lumen we believe to be due to either non-resolution of the initial inflamation of the bronchus or a subsequent distortion by the dilated air spaces." It is not difficult to conceive how a severe paroxysm of coughing may lead to the rupture of such a pneumatocele formed in the course of a bronchopneumonia, this leading to formation of spontaneous pneumothorax.

In the second variety of pneumothorax complicating pneumonia and associated with empyema, the simple pneumothorax may quickly evolve into pyopneumothorax. The pathogenesis of this variety is easily understandable as the situation resembles that of a pulmonary abscess or tuberculosis. It represents an open pneumothorax; the fistulous opening is larger, caused by the breaking down of an infected pulmonary focus, and does not close in expiration. Both varieties may be ushered in by a picture of an acute respiratory crisis, or, masked by the other grave symptoms of the underlying pneumonic process, may pass unnoticed.

Summary. 1. Spontaneous pneumothorax may occur as a complication of pneumonia in adults leading to the unwarranted suspicion of tuberculosis.

2. The literature on the subject is rather scant, containing 20 reported cases; 2 cases here presented bring the total of reported cases to 22.

3. This complication of pneumonia in adults is not commonly known and in spite of the scarcity of the reported cases probably occurs more frequently than is apparent from the review of literature. The fact that this occurrence, being masked by the other grave symptoms of the underlying pneumonic process, may not constitute a distinct or dramatic episode in the course of a pneumonia, accounts for the failure in more frequent recognition of this complication. With serial Roentgen ray studies it may be found to happen much oftener than noted heretofore.

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THE HEPATOTOXIC ACTION OF DIETHYLSTILBESTROL WITH REPORT OF A CASE

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SINCE the original publications on synthetic estrogens by Dodds and his associates[3,4] in 1938, much experimental and clinical study has been devoted to these substances, and a "vast literature" has been built up.

The therapeutic effects of one of these synthetic substances, diethylstilbestrol (4,4′-dihydroxy-a:B-diethylstilbene), were found in general to be similar to those of natural estrogens; of great import was the observation that this new agent was strongly potent when administered orally. It was further noted that various extragenital effects were produced in animals, and particular attention was focused on the liver as being especially vulnerable to fatty degeneration and necrosis.[1,8,13,14,15,18] When diethylstilbestrol was tried in humans, the implication of hepatic impairment seemed strengthened by numerous reports of unfavorable symptoms, such as nausea, vomiting, dizziness, and malaise; the incidence of such side reactions varied from 5 to 80% in different series.[5,16,19] However, after many studies of hepatic function performed by various groups employing diethylstilbestrol clinically, the general conclusion was reached that the drug was not an hepatotoxic agent when used in therapeutic doses.[6,7,9,17]

Aside from the unpleasant systemic side effects just mentioned, several severe reactions to diethylstilbestrol have been reported, most of them apparently being on an allergic basis. These include a case of exfoliative dermatitis, described by Kasselberg and Memphis;[12] a case of severe angioneurotic edema, by Saphir and Weinglass;[20] and

1 case of angioneurotic edema, 1 of herpetic eruption and 4 of mild rash associated with faintness and dizziness, by Cohen and Cohen.[2]

We present herewith a case of hepatocellular jaundice occurring after diethylstilbestrol administration. A study of this and of other cases demonstrated an allergy to be the underlying factor. To our knowledge, no similar instance of definite hepatic impairment in the human has been reported.

Case Report. H. W., a 44 year old colored female, was admitted to the Medical Service of the Metropolitan Hospital on May 26, 1942, for jaundice, nausea and epigastric pain. Eight days previously the patient had begun to experience vague epigastric pain and nausea, and 4 days later jaundice was noted, with the urine becoming dark and the stools grayish. There had been frequent episodes of "indigestion" and marked constipation during that week.

The patient had presented herself several weeks earlier at the Gynecological Clinic for complaints associated with the menopause, namely nervousness, palpitation, insomnia, hot flushes, and transitory arthralgias, all present since the early part of 1940. Diethylstilbestrol was prescribed, 1 mg. every other day, but the patient did not adhere strictly to this régime, and by the time of admission she had taken 12 mg. over a 14-day period. The nausea and epigastric discomfort were first noted 8 days, and the jaundice 12 days, after medication had been begun. Pruritus was never present.

The patient's last menstrual period occurred in December 1941. She had a 16 year old son, alive and well, and 3 miscarriages subsequent to his birth. There was also a history suggestive of gonorrheal and possibly of luetic infection at the age of 17 or 18.

TABLE 1.—LABORATORY DATA—PATIENT H. W.

Date 1942	Icterus index	Van den Bergh	Ceph. floc.	Phosphatase	Total serum prot.	Serum alb.	Serum glob.	Total serum chol.	Chol. esters	Free chol.	Kahn test	Urine		W.B.C. (thous. per c.mm.)	Other data
												Bile	Urobilin		
5-27	65.0	Biph.	4+	4.0	7.32	3.46	3.86	100	36	64	4+	Pos.	Neg.		Wass. neg.
5-29	65.0	Biph.	4+									Pos.	Neg.	4.4	
6- 3	34.0	Del.	4+	3.0	6.40	3.12	3.28	140	70	70	3+	Neg.	Incr.		Wass. neg.
6- 5	12.8	Del.	3+	3.0	8.02	2.31	5.71	85	37	48		Neg.	Incr.		
6- 8	10.8	Del.	3+	3.1	8.00	4.30	3.70	158	83	75	Neg.	Neg.	Incr.	4.5	Wass. neg.
6-10	11.9	Del.	3+	3.3	7.80	5.02	2.78	150	75	75	Neg.	Neg.	Norm.		Wass. neg.
6-24	8.1	Del.	4+	5.0	6.09	4.91	1.18	148	80	68		Neg.	Norm.		
7- 6	16.0	Del.	4+	3.7	8.02	3.17	4.85	150	80	70		Neg.	Norm.		
7-17	8.0	Neg.	Neg.	3.1	8.02	5.07	2.95	100	72	28	Neg.	Neg.	Norm.		Wass. neg.
8- 5	6.0	Neg.	Neg.	4.5	7.60	5.20	2.40	130	94	36		Neg.	Norm.		
8-10	6.5	Neg.	Neg.	4.0	6.02	4.63	1.39	100	56	44		Neg.	Norm.		
1943															
3-17	5.0	Neg.	Neg.	4.5	8.19	5.67	2.52	165	116	49	Neg.	Neg.	Norm.		Wass. neg.
4-26	5.0	Neg.	Neg.	3.9	7.83	5.04	2.79	139	99	40		Neg.	Norm.		
4-29	5.5	Neg.	Neg.	3.3	8.05	5.03	3.02	170	114	56	Neg.	Neg.	Norm.	7.3	Wass. neg.

On admission to the hospital, physical examination revealed a moderately obese middle-aged colored female appearing subacutely ill. The temperature, pulse and respiration were normal. Icterus of the skin, scleræ, and mucous membranes was distinctly perceptible. The liver edge was palpated 2 finger-breadths below the costal margin, and was somewhat tender. The spleen could not be felt. The remainder of the physical findings were not remarkable.

Course. Laboratory data obtained after admission (Table 1) presented definite evidence of diffuse intrahepatic involvement: jaundice, markedly positive cephalin flocculation, low total serum cholesterol, low percentage of cholesterol esters, and inversion of the albumin:globulin ratio. None of the

figures was characteristic, or even suggestive, of extrinsic biliary obstruction.[21] Roentgenographic studies inadvertently performed on June 11, when gross jaundice was still present and function tests indicated persistent involvement of the liver, revealed the gall bladder to be normal in size, shape and position; the test dye was well concentrated, and emptying occurred promptly following a fatty meal. There was no evidence of calculi.

The patient was treated with a diet low in fat content and high in carbohydrate, protein and vitamins, especially B-complex. This was supplemented by daily intravenous injections of 50% glucose. Clinical improvement occurred gradually, and concomitantly the laboratory findings reverted to normal. The patient left the hospital on August 5, 1942, refusing to stay until investigation of the etiologic factors responsible for her illness had been completed. A follow-up study was attempted, but the patient had disappeared. It was not until April 24, 1943, that we located her and induced her to reënter the hospital for further study. At this time she complained severely of recurrent menopausal symptomatology. There had been no further jaundice or epigastric pain.

Procedure and Discussion. In the belief that diethylstilbestrol might have been the cause of jaundice in this case, we began a systematic study. In view of the relatively small amount of drug taken by the patient, it did not seem reasonable to assume a *toxic* effect, and we were inclined to consider an allergic etiology, in accordance with the reports of Finch[5] and of Saphir and Weinglass,[20] who found positive intradermal reactions with dilute solutions of diethylstilbestrol. We therefore undertook to test our patient for sensitivity to this substance. The series of skin tests performed on her, in both 1942 and 1943, are detailed in Table 2.

TABLE 2.—SKIN TESTS DONE ON PATIENT H. W. ALL TESTS INTRADERMAL USING 0.1 CC. MATERIAL

Date	Testing material	Results
6–30–42 4–26–43	Diethylstilbestrol in corn oil*—1 mg. in 5 cc.	Negative
4–26–43	Corn oil*	Negative
4–26–43	Diethylstilbestrol propionate in corn oil*—1 mg. in 5 cc.	Negative
8– 1–42 4–26–43	Patient's own serum (fresh)	Negative
8– 1–42 5– 3–43	Patient's own serum incubated 48 hours at room temperature	Negative
8– 1–42 5– 3–43	Patient's own serum incubated 48 hours at room temperature with corn oil—equal amounts	Negative
5– 3–43	Suspension of crystalline diethylstilbestrol† in patient's own serum (1 mg. in 5 cc.) incubated 48 hours at room temperature	5 cm. wheal—red, tender, indurated
5– 3–43	Diethylstilbestrol in corn oil (1 mg. in 5 cc.), incubated 48 hours at room temperature with patient's own serum	6 cm. wheal—red, tender, indurated, with central papule → pustule in 3 days → central necrosis (see Fig. 1)

* Supplied through courtesy of Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.
† Supplied through courtesy of E. R. Squibb & Sons, New York, N. Y.

In contrast to the findings of Saphir and Weinglass, we obtained no intradermal reaction in this patient when employing diethylstilbestrol alone. However, we did encounter a very severe response after incubating the crystalline diethylstilbestrol or diethylstilbestrol in corn oil with the serum of the patient for 48 hours. Besides the local reaction described in Table 2, the patient also exhibited a systemic response characterized by malaise, fever, chilliness, and discomfort in the region of the liver. The painful wheal at the injection site (Fig. 1) attained its maximal development in 36 hours, then regressed gradually and disappeared in 6 days. All the controls—diethylstilbestrol in corn oil, corn oil alone, the patient's fresh serum alone, the patient's serum incubated alone and with corn oil—gave completely negative results.

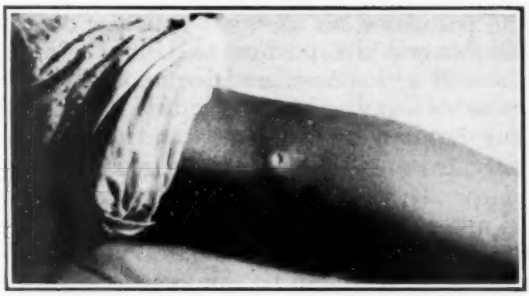

FIG. 1.—Skin reaction to diethylstilbestrol. Severity of reaction indicated by necrosis visible at center of wheal.

On the basis of these reactions, the conclusion is justified that diethylstilbestrol incubated with the patient's serum acted as an allergenic substance.

The question then arose as to whether diethylstilbestrol incubated with the sera of other patients exhibiting no clinical signs of allergy could cause similar effects in them, particularly if these patients had been treated beforehand with diethylstilbestrol. The tests undertaken to clarify this point are recorded in Table 3. It is notable that the results in all 9 patients were negative, regardless of whether they had previously taken diethylstilbestrol.

TABLE 3.—CONTROL PATIENTS—ALL TESTED WITH 0.2 CC. INTRADERMALLY OF DIETHYLSTILBESTROL IN CORN OIL INCUBATED 48 HOURS WITH PATIENT'S OWN SERUM (1 MG. IN 5 CC.)

Patient	Age	Menopausal symptoms	Oral stilbestrol taken	Result of skin test
F. M.	52	No	Never	No reaction
M. G.	45	Yes	Never	"
M. L.	40	Yes	Never	"
F. G.	52	Yes	1 mg. daily—5 mg. taken	"
G. H.	43	Yes	1 mg. daily—17 mg. taken	"
J. S.	75	No	1 mg. daily—2 mg. taken	"
M. R.	64	Yes	6 mg. (1 mg. daily) 7 days before testing	"
L. H.	58	Yes	8 mg. (1 mg. daily) 10 days before testing	"
M. M.	62	Yes	10 mg. (1 mg. daily) 4 days before testing	"

Experiments were not performed to determine whether the serum of the sensitive patient, when incubated with diethylstilbestrol, could cause a wheal in another patient, or, conversely, whether similarly prepared serum from another patient could produce a wheal in the sensitive one. Such tests might have shed light on the rôle of serum specificity as against patient susceptibility. Nevertheless, on the basis of those tests we were able to complete, it can be stated with certainty that our patient's serum, when incubated with diethylstilbestrol, had the capacity to produce an unknown substance which caused a severe local reaction as well as systemic signs similar to those occurring with the original illness.

A thorough elucidation of the findings in this case is as yet impossible, but several theoretical considerations deserve mention. Finch[5] has offered an interesting explanation for the nausea and vomiting of pregnancy; he postulated an allergic reaction of the patient to the secretion of her own gravid corpus luteum. Using this unidentified luteal hormone in cases of hyperemesis gravidarum, he obtained intradermal reactions such as we found on incubating diethylstilbestrol with serum. It is interesting that patients with nausea and vomiting due to diethylstilbestrol responded to his luteal hormone exactly as did hyperemetic pregnant women. If, however, diethylstilbestrol administration had occasioned no untoward effects, the patients exhibited *no* intradermal reaction to the luteal hormone. Conversely, Finch found that diethylstilbestrol in oil alone produced no skin reaction, just as in our case, although he could desensitize positive reactors against the luteal hormone and against diethylstilbestrol as well. He explained the tolerance of males and of young girls to diethylstilbestrol on the basis of their never having been sensitized to the luteal hormone; the tolerance of normal pregnant women he attributed to an antihormone effect of progestin.

Finch regarded diethylstilbestrol not as a toxic substance *per se*, but rather as an allergen. Although such a concept is probably correct, it might be more correct to say that only the "sensitive" patient can form the final allergenic substance in sufficient quantity to produce clinical effects. It has been proposed that the untoward reactions to diethylstilbestrol may be due to abnormal breakdown within the body. Zondek and his co-workers,[22] however, feel that normally the liver inactivates diethylstilbestrol more slowly than it does estrone, thus accounting for both the greater oral efficacy and the frequency of untoward reactions. Accordingly, they advise caution in the use of diethylstilbestrol when hepatic reserve is diminished.

The serologic findings in our case (Table 1) demonstrate that at least part of the hepatic dysfunction is manifested in disturbance of the protein fractions. This is indicated first by the positive cephalin flocculation, originally postulated by Hanger[10] as being due to abnormal globulins, but more recently[11] attributed to albumin alterations. Furthermore, although the Wassermann reaction was consistently negative, the Kahn test was strongly positive during the acute phase

of illness. Since the serum globulin fraction was at no time excessively elevated, and the albumin only moderately decreased, a *qualitative* alteration of these fractions may be the basis not only for the positive Hanger and Kahn reactions, but also for the antigen-antibody mechanism in the patient's allergic response to diethylstilbestrol.

In reporting this case of hepatocellular jaundice, we certainly have no desire to malign so valuable a substance as diethylstilbestrol. However, now that this synthetic agent is being so extensively employed for a wide variety of conditions, it seems wise to sound a warning that diethylstilbestrol in moderate dosage *can* cause severe hepatic damage in the human.

Conclusions and Summary. 1. A woman with severe hepatic damage occurring after administration of diethylstilbestrol in moderate dosage was demonstrated to be allergic to a substance formed by incubation of diethylstilbestrol with the serum of the patient.

2. All possible controls were negative. Furthermore, similarly incubated sera of other patients produced no reaction when injected intradermally in the same subjects from whom they were taken.

3. The mechanism of untoward reactions associated with diethylstilbestrol medication is discussed, and reference is made to its relationship to the toxic complications of pregnancy.

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THE ENHANCEMENT OF THE PLASMA CONCENTRATION OF PENICILLIN IN DOGS BY THE SIMULTANEOUS ADMINISTRATION OF PARA-AMINOHIPPURIC ACID, III

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This is the third of a series of papers concerning the effect of the simultaneous administration of the sodium salt of p-aminohippuric acid (PAH) and penicillin upon the plasma concentration and renal elimination of penicillin. Following the first brief announcement,[4] the second article[3] presented evidence indicating that when PAH was infused continuously by venoclysis the intravenous injection of single doses of penicillin resulted in: (1) a prolonged maintenance of a determinable plasma concentration of penicillin, and (2) a marked extension of the period during which penicillin was excreted in the urine, as well as a definite decrease in the rate of excretion and the total amount of penicillin recovered thereby per unit time.

The evidence supported the conclusion that this effect was brought about by a competition between PAH and penicillin for the same excretory mechanism of the renal tubular epithelium, since the clearance of penicillin (which normally approximates the renal plasma flow of dogs) could be depressed to or below values for the glomerular filtration rate by the simultaneous intravenous administration of PAH. The plasma concentrations of the latter compound which were found to produce this effect were above those resulting in maximal clearance values for PAH.

Toxicologic studies have indicated that this drug has an extremely low toxicity for animals. Pharmacologic investigations have shown venoclysis to be the most satisfactory mode of administration of PAH, although adequate, sustained plasma concentrations of the drug can be maintained by repeated subcutaneous or intramuscular administration, but not per os.[6a,b]

Although the earlier experiments wherein single intravenous doses of penicillin were administered showed quite adequately the inhibition of penicillin excretion by the administration of PAH, it remained for us to demonstrate the operation of this mechanism in experiments in which both penicillin and PAH were continuously infused over an extended period of time. It was thought that the continuous intravenous infusion of penicillin alone and penicillin with PAH might

yield data permitting a more accurate appraisal of the competitive affinities of these two substances for the same renal intracellular transport system and its practical importance, under laboratory conditions more closely paralleling the clinical application of the combined use of penicillin and PAH. Such experiments also would permit a histopathologic evaluation of cellular damage resulting from the use of these substances over a prolonged period of time. To this end, experiments were designed wherein penicillin alone or penicillin and PAH were infused continuously over periods of 36 to 54 hours.

Procedure. The methods for the assay of penicillin and the determination of p-aminohippuric acid, the apparatus used in the aseptic collection of urine and the general procedure in these experiments have been described in detail.[3] Very briefly, strict adherence to standard bacteriologic and surgical procedures were necessary for the collection of urine and blood samples. The modified Rammelkamp assay for penicillin[7] used in these experiments dictated these precautions.

Blood samples also were taken periodically for the determination of hemoglobin, hematocrit, plasma protein and albumin, total erythrocyte and leukocyte counts, and differential white cell counts. In the case of the earlier experiments described herein control animals, treated exactly as the test animals, except for the absence of PAH and penicillin in the infusion solutions, were maintained for the duration of the 48 hours to determine the effect of the barbiturate used to sedate the animals, water balance, the frequent bleedings, and so forth on the overall welfare of the animals. Hematologic studies, creatinine clearances, gross and microscopic tissue examinations, records of rectal temperature, heart rate, and so forth, were carried out as carefully on the control as the test animals. We found it advantageous to keep the dogs sedated by the injection of a barbiturate as frequently as indicated by the reactions of the animals to venipuncture and urine collections. Since the barbiturate caused a relaxation of the urethra, it was necessary to do a suprapubic exposure and ligation of the urethra just inferior to the neck of the bladder when the catheter was in place. This was done to avoid the extravasation of urine around the catheter.

Experimental. *Experiments Wherein Both Penicillin and PAH were infused for 48 hours.* In the first 2 experiments penicillin and PAH contained in the same infusion fluid were administered continuously by venoclysis over a period of 48 hours. The concentrations were calculated so that 15 Oxford units of penicillin and sufficient PAH to maintain the plasma concentration at about 30 mg./100 cc. were administered when the rate of infusion was 3 cc./min. This infusion fluid consisted of 1.5% sodium p-aminohippurate, 0.45% sodium chloride and 5 units/cc. of penicillin in distilled water, buffered at pH 7.4.

In both experiments, a priming dose of 120 mg./kg. of 20% sodium p-aminohippurate solution was injected intravenously. This was followed immediately by an infusion of the composition described above but containing no penicillin. After a 15-minute period for equilibration of PAH plasma concentration, a priming dose of penicillin was injected intravenously and the infusion of the solution containing both PAH and penicillin was begun. Dog 113 received 5300 units and Dog 39 received 2600 units of penicillin in the initial intravenous injections of this material. The average rate of penicillin infusion

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was determined to be 14.4 units/min. for Dog 113 and 12 units/min. for Dog 39. These rates of infusion were of a magnitude which was calculated from previous data to give plasma concentrations of pen-

TABLE 1.—RESULTS AFTER PENICILLIN AND PAH, CONTAINED IN THE SAME INFUSION FLUID, WERE ADMINISTERED CONTINUOUSLY BY VENOCLYSIS FOR THE DURATION OF THE TESTS

Hours	Penicillin plasma conc. (units/cc.)	PAH plasma conc. (mg./100 cc.)	Penicillin clearance (cc./min.)	PAH clearance (cc./min.)	Urine (vol./min.)	Penicillin progressive percentage recovery
		Dog 113, 14 kg.				
2*	.22	40.8	25.2	64.9	0.2	28.4
4*	.11	38.7	44.5	40.7	0.4	31.5
6	.09	23.1	69.4	97.3	2.3	30.3
8	.09	28.7	52.4	70.2	0.5	30.4
10	.09	26.9	175.0	152.8	3.6	32.0
12	.09	24.2	69.1	129.5	2.5	32.7
14	.09	25.1	119.9	133.5	2.9	34.2
16	.055	26.4	137.7	94.8	2.4	38.2
18	.056	23.1	84.5	69.3	1.4	42.1
20	.09	26.6	148.5	117.4	2.6	45.3
22	.09	26.0	173.8	133.4	3.3	47.9
25	.00	24.0	..	94.5	1.3	50.7
27	.055	16.7	284.9	113.6	1.7	51.8
29	.055	26.0	222.7	111.1	1.0	52.7
31	.11	27.3	169.3	90.3	2.3	58.7
33	.09	56.8	131.3	66.3	3.6	61.9
35	.09	36.5	127.3	126.0	3.4	65.0
37	.055	33.3	142.2	101.6	0.9	64.5
39	.055	29.3	189.8	63.0	1.7	64.8
41	.17	33.7	103.8	86.5	2.1	64.9
43	.17	33.4	99.7	107.1	3.7	65.7
45	.17	40.4	67.2	99.0	2.0	66.2
47	.055	38.5	103.6	93.1	2.0	65.3
48	.09	35.2	81.1	87.5	3.0	65.1
Av.	.093	30.9	122.7	97.6	2.1	65.1
		Dog 39, 14.2 kg.				
2*	.17	40.0	79.3	83.1	1.3	48.1
4	.11	35.1	108.1	105.0	2.2	59.8
6	.11	31.5	105.3	104.4	2.1	64.5
8	.088	22.1	147.5	148.4	1.2	63.6
10	.089	24.8	80.5	109.9	0.7	63.7
12	.00	28.2	..	82.3	0.6	61.9
14	.088	26.5	63.0	68.6	0.2	59.6
16	.055	30.1	187.1	87.6	0.6	59.7
18	.055	29.2	227.2	141.9	1.1	61.5
20	.055	33.5	245.0	116.9	1.3	61.4
22	.055	31.5	338.5	161.3	1.4	61.3
24	.055	27.5	160.1	123.3	1.1	60.8
26	.089	24.4	185.1	189.1	1.8	62.4
28	.088	22.4	163.1	118.1	1.0	65.1
30	.089	23.5	179.4	132.8	1.7	67.3
32	.088	25.6	135.0	118.2	4.9	68.6
34	.13	34.6	105.6	95.4	1.3	70.9
36	.089	29.2	90.0	89.3	1.7	73.0
38	.088	26.1	96.7	115.6	3.1	72.5
40	.088	30.4	116.9	78.9	1.3	72.5
42	.087	29.1	152.0	113.0	1.2	73.1
44	.088	30.0	156.0	127.6	1.3	73.7
46	.13	31.5	84.4	82.1	0.7	74.6
48	.088	28.2	54.0	62.5	0.4	74.4
Av.	.086	29.0	141.7	110.2	1.4	74.4

* Omitted from average.

icillin of about 0.025 units/cc. when no PAH was administered and about 0.1 units per cc. when sufficient PAH was infused to maintain a plasma concentration of approximately 30 mg./100 cc. A condensation of the data obtained in these 2 experiments is given in Table 1.

Before discussing the results of these experiments in any detail certain general considerations of the work should be presented. In these experiments control of the rate of infusion was obtained by regulating the number of drops of fluid which passed through the filter per minute. It is not surprising therefore that the plasma concentrations of both substances should have varied. An uncontrollable feature of the set-up was that as the rate of infusion decreased the plasma penicillin level dropped, both because of the decreased rate of infusion of the antibiotic substance and because of its increased tubular excretion, due to the fall in plasma PAH concentration. Conversely, as the rate of infusion was increased to raise the lowered PAH concentration the plasma penicillin level was increased incommensurately. This point is illustrated in the data presented in Table 1.

Considering the data on both dogs together, several points appear to have been established satisfactorily. As long as the rate of infusion was kept constant, judging by the PAH plasma concentration, the penicillin plasma concentration remained at about 0.09 units/cc. (Dog 113) or slightly below that in Dog 39 where the rate of infusion was correspondingly less (12 units/cc.). The plasma concentration varied somewhat as might be expected considering the method of rate control, the type of assay, and the effect of PAH on penicillin clearance.

The penicillin clearance was usually greater than the glomerular filtration rates for the animals (81.1 cc./min. for Dog 113 and 78.2 cc./min. for Dog 39), but approximated the minimal renal plasma flow of such animals only in a few instances at which time the plasma concentration of penicillin was also decreased. Thus the tubular excretion of penicillin was diminished but not abolished by PAH, except possibly at the beginning of the experiments.

At very low plasma concentration the renal clearance of PAH approximates the minimal renal plasma flow of man[9] and dogs,[5] which in the latter instance exceeds 200 cc./min. for animals of this weight. However, as the load on the tubules is increased by raising the plasma concentration of PAH its renal clearance is suppressed as is the case in these data.

It may be noted that the urine flow did not equal consistently the rate of infusion. This was due in part to the amount of sodium chloride that was added to the fluid in addition to the sodium p-aminohippurate and penicillin-sodium. It follows that the obvious, and actually the most important, finding before and after autopsy was tissue edema.

In these 2 dogs, 65.1 and 74.4% of the penicillin injected appeared in the urine during the course of the experiment. Of this amount, 28.4 and 48.1% was excreted in the first 2 hours following the priming doses in the course of the progressive recoveries. More important

than the actual figures is the fact that not all of that which was injected was ultimately recovered, which probably means that a certain amount of the material was inactivated or eliminated by another route. This observation is in confirmation of the earlier reports of Abraham, Florey and associates,[1] Rammelkamp and Keefer[8] and ourselves.[3]

The hematologic and toxicologic findings in all the experiments will be considered together, later in this report.

The effect of increasing the rate of infusion of penicillin on plasma concentration and clearance of the antibiotic substance, 36-hour experiments. The purposes of these tests were to determine the effect of increasing the rate of infusion of penicillin on its plasma concentration and also the actual plasma values obtained when penicillin was infused at different rates, in addition to serving as toxicologic controls on the 48-hour PAH experiments.

The experiments were designed so that an initial intravenous injection of 1000 Oxford units of penicillin was immediately followed by the intravenous infusion at 15 units/min. of penicillin in a solution containing 0.22% NaCl and 3.75% glucose. This was injected at a rate of 1 cc. per minute with the aid of an electrically driven mechanical injection apparatus. The same solution containing no penicillin was infused at a different site by "drip" at a rate of 2 cc./min. Thus the same vol./min. was injected in all the experiments. Duplicate creatinine clearances were performed every 12 hours during the experiments. The initial (15 units/ min.) rate of infusion was maintained for 16 hours to permit more than adequate time for equilibration of the plasma concentration. Immediately after the 16-hour clearance, the concentration of penicillin in the infusion was doubled to permit the infusion of 30 units/cc./min. Ten hours later the concentration of penicillin in the infusion solutions was doubled again so that for the last 10 hours of the experiment the rate of infusion was 60 units/cc./min.

Unfortunately, the conditions under which this set of experiments were performed were sufficiently different from those obtained during the other types of experiments as to make these useless as quantitative controls on the previous ones in which penicillin and PAH were infused together. Because of the uniformity of the electrically driven infusion of penicillin, these dogs received a greater average amount of penicillin at a more regular rate than in the previous experiments. Moreover, there is reason to believe that a faulty standard penicillin solution was employed to set the values in the penicillin assays. These facts, though minimizing the comparative usefulness of the first 16 hours of these experiments, do not invalidate the differences resulting from increasing the dosage of penicillin within these experiments.

A condensation of the data is presented in Table 2. Increasing the rate of infusion of penicillin from 15 to 30 units per minute increased the plasma concentration of the antibiotic agent in all 3 experiments. Considering average values alone, there was a twofold or greater increase in the plasma penicillin concentration when the rate of infusion was increased from 15 to 30 units per minute. A second increase in

TABLE 2.—RESULTS AFTER A SUMMARY OF DATA ON EXPERIMENTS WHEREIN PENICILLIN, ADMINISTERED CONTINUOUSLY BY VENOCLYSIS, WAS INCREASED PERIODICALLY BY DOUBLING ITS CONCENTRATION IN THE INFUSION FLUID

Hours	Dog 86, 13.6 kg.			Dog 117, 20.5 kg.			Dog 102, 18.6 kg.		
	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)
Initial Intravenous Injection = 1000 Units of Penicillin. Rate of Continuous Infusion = 15 Units/Min.									
1*	.130	126.7	0.2	.074	97.0	0.8	.090	321.1	0.4
2	.089	121.5	4.5	.038	87.9	0.7	.041	334.1	0.3
4	.045	452.9	3.9	.037	270.0	0.9	.210*	85.3*	3.3
6	.090	108.2	2.4	.037	..	..	.093	193.5	0.9
8	.045	194.0	1.8	.036	260.0	1.5	.093	224.7	1.3
10	.094	128.7	1.4	.037	464.1	3.6	.093	136.6	1.9
12	.092	98.8	2.4	.037	255.0	1.0	.093	481.7	3.0
14	.043	206.5	0.9	.035	330.8	0.8	.042	91.4	0.2
16	.044	284.9	1.8	.037	348.6	1.6	.094	112.8	2.8
Av.	.068	199.4	2.4	.037	288.1	1.4	.078	225.0	1.7
Rate of Continuous Intravenous Infusion Increased to 30 Units/Min.									
18	.130	161.2	2.7	.160	161.2	4.7	.146	171.9	5.2
20	.190	130.2	1.8	.110	231.1	1.6	.047*	223.2	0.4
22	.140	281.6	2.4	.150	151.7	1.2	.146	243.7	0.9
24	.160	439.8	5.5	.160	183.4	3.2	.137	148.1	1.6
26	.086	339.5	2.4	.140	126.0	0.5	.125	205.1	3.7
Av.	.141	270.5	3.0	.140	170.7	2.2	.139	198.4	2.4
Rate of Continuous Intravenous Infusion Increased to 60 Units/Min.									
28	.190	438.0	2.3	.190*	227.7	1.1	.185	256.2	3.5
30	.180	487.7	3.1	.190*	177.4	1.2	.143	259.3	2.8
32	.180	591.7	1.0	.300	151.1	2.3	.190	252.1	0.9
34	.190	559.5	2.1	.300	262.2	1.0	.281	195.3	1.3
36	.210	328.0	0.8	.310	252.3	0.9	.210	204.4	0.6
Av.	.190	481.0	1.9	.300	214.1	1.3	.202	233.5	1.8

* Omitted from averages.

the rate of infusion from 30 to 60 units per minute likewise increased the plasma concentration of penicillin in all the experiments, but doubled the value in a single experiment. The clearance data indicated that the capacity of the renal tubular epithelium to remove completely penicillin from the plasma supplied to them was not exceeded in any of these experiments, for there was no depression in the clearance of penicillin as the plasma concentration was raised or the amount infused per minute was quadrupled.

Sufficient data are presented that one may calculate the amount of penicillin excreted per unit time. By doing so it can be shown that except for Dog 117, as the rate of infusion was doubled, the amount of penicillin excreted per minute was approximately doubled. The glomerular filtration rates (creatinine clearance) of the dogs did not vary significantly during the experiments.

The effect of increasing the plasma concentration of PAH on the plasma concentration of penicillin when the rate of infusion of penicillin remained constant. Since these were probably the most critical of our animal experiments, from the standpoint of clinical significance, it is proper that they should be presented last in the overall program of the penicillin-PAH research on dogs. A study of the accompanying figures, 1 through 4, will reveal the nature of the experiments. In concept they consisted of a control equilibrium phase wherein penicillin but no PAH was infused, followed by steplike periods of increasing PAH plasma concentration. Finally, the PAH plasma concentration was allowed to fall by discontinuing its injection. During the whole of the experiments the rate and unitage of penicillin injected remained constant.

In more detail, the infusion fluid contained in addition to penicillin or sodium p-aminohippurate 0.22% sodium chloride and 3.75% gluclose. Penicillin was added to a portion of the infusion fluid and was injected by an electrically driven instrument delivering 1 cc./min. which contained 15 units of penicillin. The solution containing no PAH was infused by "drip" at a rate of 2 cc./min. during the control portion of the experiments. To this the amount of sodium p-aminohippurate necessary to produce the desired plasma concentration was added. The control period was 18 hours in one experiment and 20 hours in the other. The duration of injection of PAH to produce a given plasma level varied from 8 to 12 hours. To establish the various plasma levels of PAH single priming doses of 20% concentration were injected immediately after the last clearance at the preceding level. Thus the plasma levels were quickly increased, the concentrations of PAH in the infusion fluid being just the amount necessary to maintain the level at the desired plane. The data on the first of these experiments are presented in Figures 1 and 2. The data on the second experiment are presented in Figures 3 and 4.

The priming dose of penicillin in the first test (Dog 63) was 5000 units and the actual rate of infusion was 13.3 units/min. instead of the calculated 15 units/min. Probably because of the high priming dose a period of 12 hours was necessary in the case of Dog 63 (Fig. 1) before

the basal plasma concentration of about 0.025 units of penicillin/cc. was attained. Once attained it remained constant for at least 6 hours. During the first 2 hours after the infusion of PAH was begun the plasma concentration increased to 0.062 units/cc. where it remained constant as the plasma concentration of PAH was maintained at about 30 mg./100 cc. In the next period lasting from the 26th to the 36th hour of the experiment the PAH plasma concentration was increased to 80 ± 10 mg./100 cc. There was a concomitant increase in the penicillin plasma concentration to 0.089 units/cc. In the final period the concentration of PAH was increased to 110 ± 5 mg./100 cc. There was a lag of 4 hours before the penicillin plasma concentration began to rise again but it had attained a concentration of 0.17 units/cc. at the time the infusion of PAH was discontinued. As soon as the PAH was stopped the plasma concentration of both compounds began

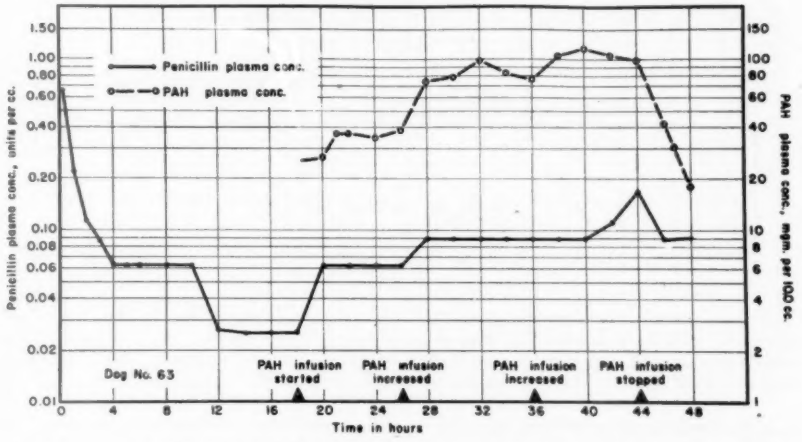

FIG. 1.—The effect of a stepwise increase in the p-aminohippuric acid plasma concentration on the level of penicillin in the plasma when it was administered continuously by venoclysis at a constant rate of 13.3 units/minute. The initial intravenous priming dose of penicillin-sodium was 5000 Oxford units. Dog 63.

to fall. The maximal penicillin plasma concentration attained was about 7 times the basal value when penicillin was infused alone.

Figure 2 shows the renal clearances of both PAH and penicillin during the course of the 48-hour experiments on Dog 63. We have frequently noted more or less cyclic fluctuations in the clearance of penicillin during these long-term experiments. These fluctuations were not necessarily associated with similar changes in urine flow. They were most exaggerated in the control phase of these experiments yet were perceptible even when PAH suppressed the overall clearance of penicillin. These changes were not associated with the administration of barbiturate and cannot be accounted for by errors in technique.

The administration of PAH depressed very strikingly the clearance of penicillin and tended to minimize its fluctuations. In general, as

the plasma concentration of PAH was increased the fluctuations in penicillin clearance decreased as did its maximal clearance within a given period. Also, as the PAH plasma concentration was raised its clearance decreased gradually. Again, it may be noted that on the whole these changes were independent of urine flow.

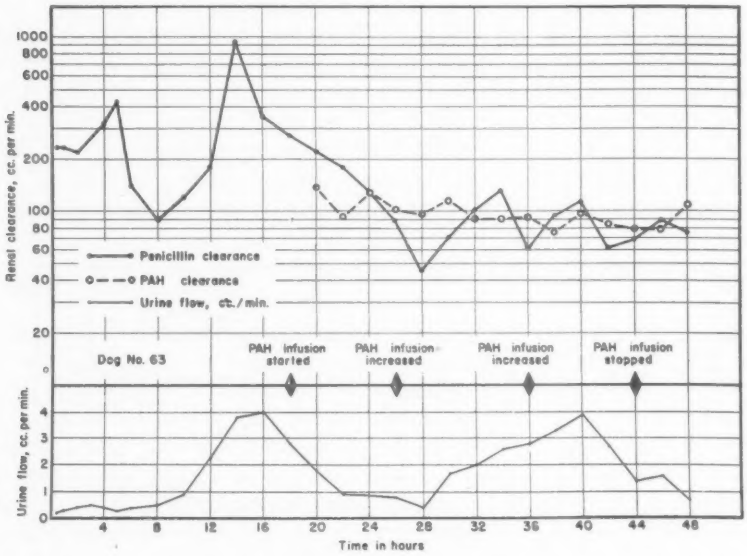

FIG. 2.—Renal clearance and urine flow data corresponding to the plasma level data presented in Figure 1, showing that as the plasma concentration of p-aminohippuric acid was elevated stepwise the clearance of penicillin was markedly depressed and remained at a low level for the remainder of the experiment. Dog 63.

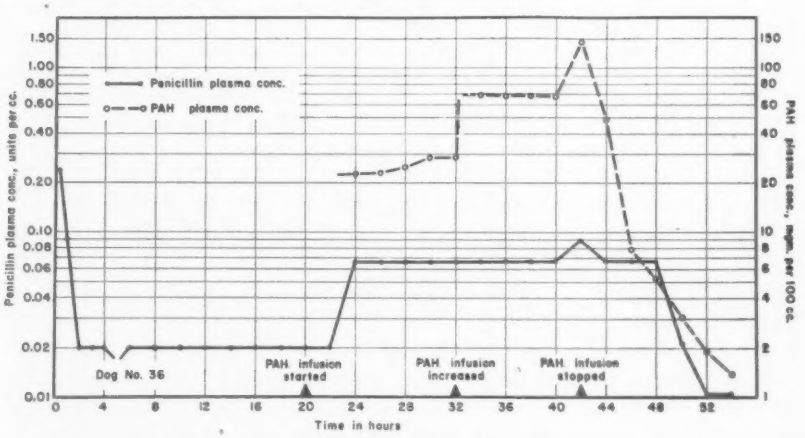

FIG. 3.—The effect of a stepwise increase in the p-aminophippuric acid plasma concentration on the level of penicillin in the plasma when it was administered continuously at a rate of 14.79 units/minute. The initial intravenous priming dose of penicillin sodium was 2500 Oxford units. Note that at the end of the experiment the plasma concentration of penicillin remained elevated until the plasma PAH concentration fell below 8 mg./100 cc., after which time it fell precipitously. Dog 36.

In the experiment on Dog 36 (Figs. 3 and 4) the priming dose of penicillin was decreased to 2500 units and the rate of infusion was 14.79 units per minute. It may be seen in Figure 3 that the period for the attainment of equilibrium in the control phase of the experiment was much shorter. For 20 hours, except for a technical error at the 5-hour period the plasma concentration was maintained at 0.02 unit/cc. when the rate of infusion was 14.79 units per minute. As soon as a plasma PAH concentration of 25 ± 3 mg./100 cc. was attained the penicillin level in the plasma rose from 0.02 to 0.66 units/cc., more than a threefold increase. This was maintained for a period

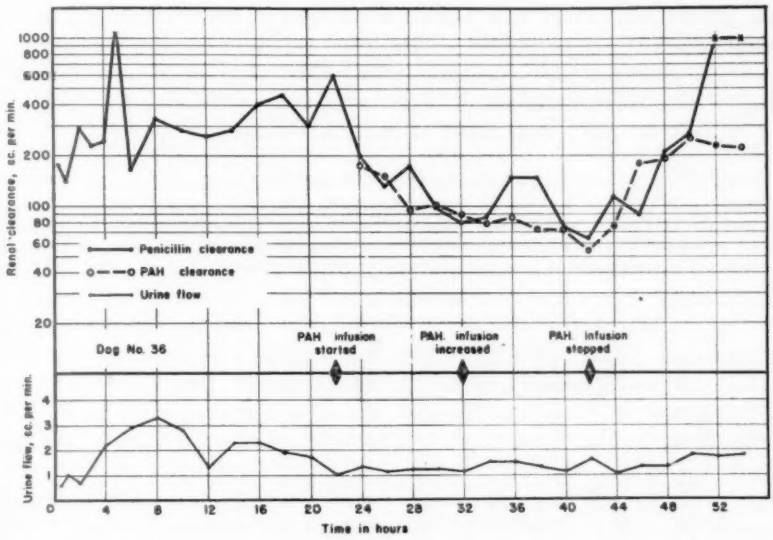

FIG. 4.—Renal clearance and urine flow data corresponding to the plasma level data presented in Figure 3, showing that as the p-aminohippuric acid plasma concentration was elevated stepwise the clearance of penicillin was markedly depressed and remained low until after the infusion of PAH was stopped. As the plasma concentration of PAH fell the clearance of both PAH and penicillin rose rapidly until they approximated renal plasma flow. The last two values for penicillin clearance could not be calculated since its plasma concentration was below the limits of the assay. Dog 36.

of 12 hours. A further increase in PAH plasma level to 68 ± 1 mg./100 cc. did not increase the penicillin content in the plasma. Inadvertently, the plasma PAH concentration was markedly increased to about 145 mg./100 cc. at the end of the last 2-hour period of the PAH infusion. At that time the penicillin plasma level promptly increased to 0.089 units/cc.

This experiment was extended and penicillin administration was continued beyond the termination of the PAH infusion to follow the fall of the PAH plasma concentration and to determine the effect of that fall on the level of penicillin in the plasma. It may be seen that except for a prompt initial drop there was a lag period before the penicillin plasma concentration fell. However, 10 hours after the PAH was stopped (the 52-hour period) no penicillin was detectable

in the plasma and this was confirmed in the last 2 bleedings of the experiment. Thus the experiment demonstrated that we could both raise and lower the penicillin concentration of the plasma by raising and lowering the PAH plasma level, even when the rate of infusion of penicillin was maintained at such a low point as to produce only a barely determinable plasma concentration of the agent when no PAH was administered.

The curves presented in Figure 4 concerning the penicillin and PAH renal clearances are entirely consistent with the plasma findings shown in Table 3. During the control phase the clearance of penicillin fluctuated but was almost uniformly about 225 cc./min. As soon as the infusion of PAH was begun there was a precipitous fall in the renal clearance of penicillin. The trend of the penicillin clearance as well as PAH clearance continued downward as the plasma concentration of the latter compound was increased, reaching a low point of 54 cc./min. at the termination of the PAH infusion.

TABLE 3.—HEMATOLOGIC DATA

Some dogs received both penicillin and sodium p-aminohippurate continuously by venoclysis for a period of 48 hours; others received an infusion of penicillin for 36 hours; their corresponding controls received the infusion fluid without either penicillin or sodium p-aminohippurate acid for a similar period of time.

Dog No.	Hours*	Hemoglobin (gm./100 cc.)	Erythrocytes (millions)	Leukocytes (thousands)	Hematocrit (%)	Plasma protein (gm./100 cc.)	Plasma albumin (gm./100 cc.)	Remarks
81	0	15.0	6.9	19.0	51	6.6	..	Control dog with Dog 113
	24	11.4	5.4	22.4	39	5.5	2.5	
	48	10.2	4.4	16.4	33	4.9	2.3	
113	0	14.2	5.9	9.0	42	8.0	..	Received continuous intravenous injection of PAH and penicillin
	24	14.1	6.0	13.2	50	4.4	2.6	
	48	12.6	5.5	15.7	40	3.7	2.0	
114	0	10.2	4.8	10.6	38	7.0	2.5	Control dog with Dog 39
	24	8.0	3.8	36.8	29	5.6	1.7	
	48	9.8	3.8	24.0	30	5.2	1.5	
39	0	15.7	7.5	5.8	53	5.8	4.0	Received continuous intravenous injection of PAH and penicillin
	24	12.6	6.1	16.9	40	4.6	2.9	
	48	12.7	5.2	10.7	39	3.9	2.2	
86	0	14.8	7.5	20.0	48	5.9	3.7	Control dog with Dog 102
	24	15.1	7.3	20.2	51	5.8	3.8	
	36	14.4	6.2	14.0	46	5.7	3.1	
102	0	16.3	7.1	9.4	51	5.6	3.8	Received continuous intravenous injection of penicillin for 36 hours
	24	12.4	5.8	17.9	44	4.9	3.0	
	36	13.7	6.5	17.5	47	3.8	2.1	

* Hours after the experiment was begun at which the heparinized sample of blood was removed by venipuncture.

The clearances during the last 12 hours were proof, in our opinion, that there was no impairment of renal function by the materials administered during the experiment. It should be noted that as the plasma PAH level fell the clearance of both penicillin and PAH rose. The last determinable clearance of penicillin was 270 cc./min. at which time the clearance of PAH was 225 cc./min. The clearances of PAH during the last 2 periods of the experiment were 230 and 225 cc./min.

We believe that these values, together with the unaltered glomerular filtration rate, are the best possible evidence that can be offered for the absence of functional renal damage in these experiments, since they indicate that the ability of the tubules to clear completely the plasma of penicillin and PAH at low concentrations has not been impaired and that there was also no impairment of glomerular filtration, as evidenced by creatinine clearances.

Toxicity. The gross and microscopic findings in these and the corresponding control animals have been considered in some detail in another communication in this series.[6b] However, certain of the data can be presented more properly at this time. Table 3 presents condensations of hematologic studies on some of these dogs during the course of the experiments. When one considers the nature of the experiments, the greater input than output of fluids, the removal of up to 185 cc. of blood during the 48 hours, the numerous operative procedures that were carried out, and so forth, it is remarkable that the changes were no greater than observed. Hemoglobin values dropped in some cases and increased in other experiments. The greatest fall occurred in a control dog which received neither penicillin nor PAH. Also, the hematocrit decreased more in a control dog than in those which received penicillin and PAH. Total plasma proteins and albumin decreased in all the experiments which was not surprising considering the dilution effect and their removal by bleeding. A leukocytosis occurred in all the animals which was actually an increase in neutrophilic cells, resulting in a relative lymphocytopenia. This effect may be due partially to the wounds produced by surgery and possibly also by pyrogenic influences, such as the localized application of heat by means of an electric hot pad used to maintain proper body temperature.

As has been stated before, the most outstanding and only significant finding resulting from the experimentation was definite tissue edema. This was decreased somewhat by attention to the electrolyte content and the tonicity of the infusion fluids. The infusion rate of 3 cc./min. was in excess of the urine flow the dogs could maintain over a period of time but was deliberately used to minimize fluctuations in the PAH plasma concentration since we were forced to use a "drip" infusion method for the administration of that compound and also to avoid the use of unnecessarily hypertonic solutions when the plasma level of PAH was maintained at very high levels. Definite pathologic findings in the unselected dogs such as focal subcapsular renal abscesses and infectious granulomatous lesions were as frequent in the control as in the test animals and were not considered as being due to or influencing the experiments. A detailed description of the histopathologic findings will be described in the fourth report of this series.[6b]

Microscopic examination of the urine present in the bladder, ureters and renal pelvis, and in the urine that had been allowed to stand in the refrigerator overnight, did not reveal the presence of crystals of p-aminohippuric acid or its sodium salt. The histologic sections of the kidneys gave no evidence of the blocking of tubules by crystals,

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Comment. In these experiments we have attempted to simulate as closely as practicable in the laboratory the initial clinical evaluation of the combined use of penicillin and sodium p-aminohippurate. Being animal experiments, they have permitted us a more convenient medium for a very critical analysis of the pharmacodynamics of this form of therapy and a much more thorough check on the possible toxicologic effects to be anticipated in the clinical use of these combined materials. Moreover, they have served as a basis and justification for the initial combined use of penicillin and sodium p-aminohippurate in patients, reported elsewhere.[2]

We have found no evidence that the competitive tubular excretion of these two substances is on any basis other than physiologic. Therefore we have visualized the process as one involving a common transport system across the renal tubules in which the competition between penicillin and PAH for this common carrier is very likely one of mass action, and in which relative affinities of the two substrates for the same system play an undetermined rôle. It must be realized that the whole competitive process is a dynamic one which rapidly shifts as the plasma concentration of either component is varied within certain limits. All our evidence, functional and histomorphologic, substantiates this physiologic explanation which we have offered.

Summary. In these experiments it was shown that the combined intravenous administration of penicillin and sodium p-aminohippurate could be carried out continuously over a period of at least 48 hours without the occurrence of morphologic or functional changes directly attributable to these two compounds.

The intravenous administration of PAH to maintain plasma concentrations of about 30 mg./100 cc. invariably resulted in an increase in penicillin plasma concentration of from $2\frac{1}{2}$ to 4 times the basal level, even though the concentration of penicillin was not varied. The stepwise increase in plasma PAH concentration above the level of 30 mg./100 cc. resulted in a further elevation of the penicillin plasma level although this was not a commensurate increase.

The effect of PAH in increasing the plasma concentration of penicillin was always reflected in a decrease in the renal clearance of penicillin.

Since PAH could not be demonstrated to be nephrotoxic by any method which we used, these findings support the concept that the effect of this compound is purely one of physiologic competition with penicillin for a common renal tubular excretory mechanism.

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THE ANTISTAPHYLOCOCCAL ACTIVITY OF VARIOUS SULFONAMIDES

WITH A METHOD FOR ROUTINE DETERMINATION OF CHEMOTHERAPEUTIC ACTIVITY*

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THE antistaphylococcal activity of the sulfonamides in actual clinical use has not been compared *in vivo* on a quantitative basis so far. This is due perhaps to the difficulties often encountered in producing experimental infections with *Staphylococcus aureus* which are lethal for untreated animals but still sensitive to treatment with chemotherapeutic agents. Numerous authors used the intravenous,[1,7,8,10,13] subcutaneous,[18] or intraperitoneal[5,6] injection of heavy inocula of staphylococci for chemotherapeutic studies in mice. This heavy infection responded only to high doses of sulfonamides, and in many cases the effect was limited to a delay of the death of the animals. In other cases, a high ratio of the surviving animals was not cured but developed chronic infections.[1,8] Such results led to the opinion that the experimental staphylococcus infection is less sensitive to chemotherapeutic treatment than other coccic infections.[8]

The use of mucin for the intraperitoneal infection of staphylococci, recommended by Buttle,[4] improved the technique of infection and the results of the chemotherapeutic tests. This method apparently is now widely used.[3,9,12,14,15,17]

Different strains of staphylococcus tested in this laboratory proved to be highly virulent for mice if injected in a suspension of mucin. The infections produced with these strains were used for an extensive comparison of the antistaphylococcal activity of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine; the results of these experiments and the observations on infection and therapeutic activity are presented in this paper.

* An abstract of this paper was presented at the 45th Meeting of the Society of American Bacteriologists, New York City, May 1944.

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Methods. Seven strains of *Staph. aureus* have been tested. Strains No. 6339, 6340, 6342 and 6343, isolated from humans, were obtained from the American Type Culture Collection. Staph. 209 is the standard strain used by the Food and Drug Administration for the evaluation of disinfectants. Staph. Zorn was given to us by Dr. E. Bliss.* Staph. B8 was isolated in our laboratory from a boil. All these strains possess the classical cultural and morphologic characteristics of *Staph. aureus*. Their toxin production was low on the media used.

For stock cultures, 6 hours growth on blood agar slants was prepared and kept in the ice-box. At the beginning of this investigation, fresh cultures were made once or twice weekly. Later, it was found that these strains keep their virulence for long periods (up to 1 year) if stored in the refrigerator; since then, stock cultures have been prepared once monthly. Attempts to obtain a consistent infection of mice with cultures in liquid or semisolid media were unsuccessful. Satisfactory results were obtained by the use of suspensions from agar slants. For the infection, a 15-hour culture on blood agar slants was prepared. The growth was suspended in 5 cc. broth, which was diluted to a constant turbidity. We used a turbidity giving 60% light transmission on the Fisher Electrophotometer, Mod. A.C., Filter A. Suspensions of the desired turbidity were diluted thereafter to 10^{-6} in broth, and plate counts were made by means of a Quebec Colony counter. The counts of the suspensions so obtained were sufficiently uniform (200 to 700 cells in 1 cc. of a 10^{-6} dilution). Mice were infected intra-abdominally with 1 cc. of the 10^{-4} dilution in 5% mucin (without glucose). The 10^{-4} mucin suspension contained an average of 50,000 cells.

Experiments were conducted on 40 to 100 mice, divided in groups of 5 to 10 mice for each dose and each preparation tested. Untreated control mice died within 24 hours, only occasionally (5 to 10%) 30 to 70 hours after infection. The behavior of the surviving treated animals was closely followed. The observation period was reduced from 60 to 90 days to 21 to 30 days when it appeared with certainty that deaths after the 14th day occurred only in a negligible number of mice. Succumbing untreated and treated animals were autopsied, and heart cultures were routinely made; often peritoneal smears were also taken. Surviving mice were killed at various intervals after infection, and organ cultures of lung, liver, spleen, kidney and heart were made on blood agar plates.

Experimental. 1. The Virulence for Mice of Staphylococcus Strains in Mucin. Virulence titrations of the 7 strains used in our experiments are set forth in Table 1. All strains proved to be of satisfactory virulence.

Table 1.—Mouse Virulence of S. aureus Strains
(Intraperitoneal injection with mucin, 1 cc.)

No. of staphylococci injected	Staph. 6339	Staph. 6340	Staph. 6342	Staph. 6343	Staph. Zorn	Staph. 209	Staph. B8
Less than 10	7/12*	21/34		2/2	0/2	11/22	0/5
30-120	7/14	20/36	2/4	6/10	0/4	14/23	8/13
250-1200	14/23	51/76	5/5	3/5	4/10	17/30	22/25
2000-11,000	32/40	105/123	14/14	10/12	3/6	20/20	14/15
40,000-60,000	188/191	312/317		9/9	11/11	21/22	15/15

* 7 mice died out of 12 injected.

Four of the 7 strains killed 80 to 100% of the infected animals if 2000 to 11,000 cells were injected. Three strains showed this rate of mortality with doses of 250 to 1200 staphylococci. All strains but

* We are indebted to Dr. Bliss for this strain and for information on the technique used in her laboratory.

1 (Staph. Zorn) killed at least 50 to 60% of the infected animals if 100 staphylococci or less were given. It seems noteworthy that the virulence of an old laboratory strain, *e. g.*, Staph. 209, was not lower than that of a recently isolated strain, such as B8.

The virulence of these strains was largely dependent on the amount of mucin injected with the inoculum. It is shown in Table 2 that by decreasing the amount of mucin under 0.5 cc., a considerable drop in the incidence of fatal infection was observed.

TABLE 2.—INFLUENCE OF MUCIN VOLUME INJECTED ON THE VIRULENCE OF S. AUREUS 6340
(Intraperitoneal injection of 34,000 to 78,000 cells in 5% mucin)

Volume mucin:	0.1 cc.	0.25 cc.	0.5 cc.	0.75 cc.	1 cc.
No. of mice injected	3	6	6	3	10
No. of mice died	0	2	4	3	10

Injection with mucin results in spreading from the site of the infection, as reported for meningococcus by Miller and Castles.[11] Cultures of blood collected from the tail and cultures from heart and lungs showed that these organs were invaded ½ to 1 hour after intraperitoneal inoculation of 30,000 to 50,000 staphylococci in mucin; the growth became particularly abundant after 2 to 3 hours. The peripheral blood cultures showed occasionally isolated staphylococci during the first 10 hours after inoculation; but heavy growth was observed only after 18 to 24 hours, when the mice were already dying. This might have been due to the method in which only very small amounts of blood were used.

No spreading was observed if the same dose of 30,000 to 50,000 staphylococci was suspended in broth and injected intraperitoneally. Blood agar plate cultures from lungs and heart of mice taken at frequent intervals for the first 24 hours were negative. The organ cultures remained negative even after increasing the dose of infection to a count of 1 million.

The intra-abdominal route of infection with mucin proved to be the most reliable one. Experiments carried out with Staph. 6340 indicated that the subcutaneous as well as the intravenous injections were less satisfactory. Thirty million cells injected subcutaneously were always tolerated (80 mice). The MLD by subcutaneous injection consisted in 500 million cocci; by intravenous injection, at least 60 million cocci were required.

2. THERAPEUTIC EXPERIMENTS. The majority of the experiments by which the minimal active dose of the different sulfonamides was evaluated were done with Staph. 6340. This strain has been selected for routine determinations because its virulence was the most constant of the strains tested.

(*a*) *Results of Repeated Treatment.* Repeated treatment is commonly considered essential in testing of sulfonamides. This mode of treatment was used for the first comparison of antistaphylococcal activity of sulfonamides. In Table 3, the results are given. It appears that the minimal active dose—expressed as total dose per kg. body weight—for sulfadiazine is 0.175 gm.; for sulfathiazole, 0.350 gm.;

for sulfapyridine, 0.525 gm.; and for sulfanilamide, 1.75 gm. Surprisingly, the results with higher doses were less good. In order to clear this point, mice injected with mucin alone (without infection) were treated with sulfapyridine and sulfathiazole. It was found that the tolerance to these drugs is greatly decreased in mucin-treated animals. For instance, sulfathiazole killed mice previously injected with mucin in daily doses of 2 gm./kg., while normal mice tolerated daily doses of 10 to 15 gm./kg. It seems evident that mice treated repeatedly with high doses died of a combined toxic effect due to mucin, infection and drug. They showed staphylococci in their organs, indicating that death had occurred before the drug exerted its activity.

TABLE 3.—CHEMOTHERAPEUTIC ACTIVITY OF SULFONAMIDES IN THE S. AUREUS INFECTION WITH STRAIN 6340
(Repeated oral treatment, 7 times)

Single dose in mg./20 gm. mouse	Sulfanilamide		Sulfathiazole		Sulfapyridine		Sulfadiazine	
	Mice	Survivors	Mice	Survivors	Mice	Survivors	Mice	Survivors
0.10	..	..	..	..	..	..	5	0
0.25	..	..	..	..	..	..	5	2
0.50	..	..	20	5	10	1	19	14
1.00	..	..	15	8	14	5	5	5
2.50	10	5	27	23	34	17	5	3
5.00	10	6	10	8	22	13	10	10
7.50	..	..	..	..	9	9		
10.00	10	6	10	4	14	8	5	4
20.00	..	..	10	3	15	5	5	3

(*b*) *Results of Single Treatment.* In order to avoid the interference of toxicity, it was tried to reduce not only the dose but also the frequency of treatments. It has been found that a single treatment is sufficient to control the infection. This is shown in Table 4. The active doses by single treatment are: 0.050 gm./kg. for sulfadiazine, 0.250 for sulfathiazole, 0.375 for sulfapyridine. By this way of treatment, the phenomenon of "optimal dose" disappeared for sulfathiazole, sulfadiazine and sulfapyridine; the minimal active dose of sulfanilamide was not reached.

TABLE 4.—CHEMOTHERAPEUTIC ACTIVITY OF SULFONAMIDES IN THE S. AUREUS INFECTION WITH STRAIN 6340
(Single oral treatment)

Single dose in mg./20 gm. mouse	Sulfanilamide		Sulfathiazole		Sulfapyridine		Sulfadiazine	
	Mice	Survivors	Mice	Survivors	Mice	Survivors	Mice	Survivors
(Controls)	317	5						
0.10	..	..	..	..	..	..	5	0
0.25	..	..	..	..	..	..	5	1
0.50	..	..	..	..	..	..	44	17
1.00	..	..	..	..	..	..	55	36
2.50	..	..	25	2	25	0	25	24
5.00	10	1	48	21	20	6	18	18
7.50	..	..	40	26	44	29		
10.00	40	8	10	8	15	11		
20–30	20	5	10	8	10	9		

The sensitivity of strains 209, B8, 6339 and 6343 to sulfonamide treatment was about the same as that of Staph. 6340: single oral

doses of 0.5 to 1 mg./20 gm. sulfadiazine protected the majority of the infected mice (Fig. 1).

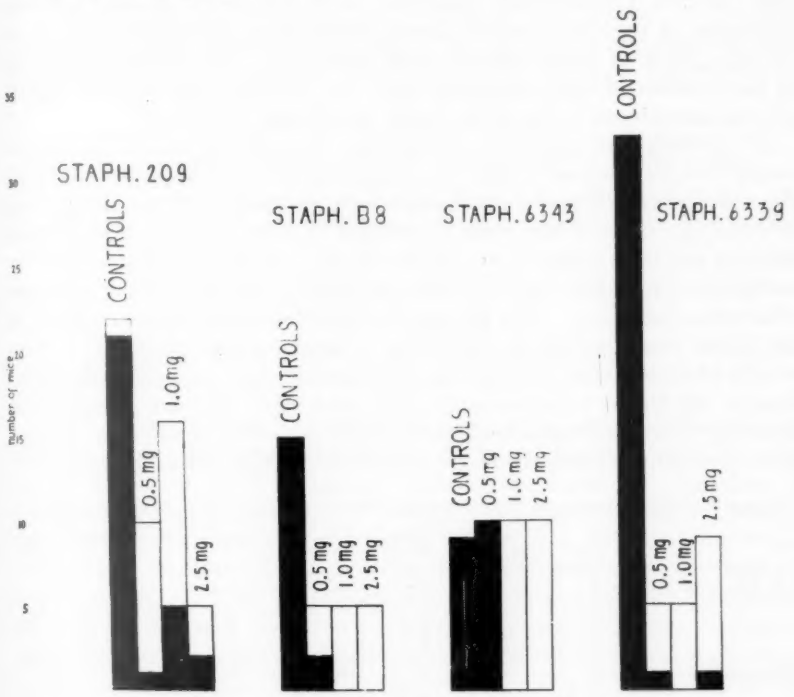

FIG. 1.—Single treatment with sulfadiazine.

(c) *Fate of the Survivors.* Mice surviving the infection after treatment have been sacrificed and autopsied at various intervals. A total number of 179 complete autopsies has been performed, and cultures of liver, spleen, lungs, kidneys, and heart on blood agar plate were made. The data obtained on survivors of infection with Staph. 6340 are given in Table 5.

TABLE 5.—ORGAN CULTURES OF MICE INFECTED WITH 1000–10,000 L.D. S. AUREUS 6340, TREATED WITH SULFONAMIDES

Kind of sulfonamide	Dose per 20 gm. mouse	No. survivors/ No. treated	4–13 days after infection organ cultures +	4–13 days after infection organ cultures −	22–120 days after infection organ cultures +	22–120 days after infection organ cultures −	Total organ cultures +	Total organ cultures −
Sulfanilamide	10 mg. single	8/15	..	4	1	2	1	12
	10 mg. repeated*	6/10	..	..	..	6		
Sulfapyridine	5–10 mg. single	37/49	2	10	3	15	10	32
	2.5–10 mg. repeated	15/24	..	2	5	5		
Sulfathiazole	2.5–10 mg. single	36/54	2	10	2	14	5	40
	0.5–10 mg. repeated	29/40	1	4	..	12		
Sulfadiazine	0.5–2.5 mg. single	26/40	7	5	2	9	15	30
	5 mg. single	17/20	..	2	2	6		
	0.5–1 mg. repeated	17/20	4	..	..	8		

* 7 treatments.

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It appears that the majority (70%) of mice surviving the infection after treatment with sulfonamides is completely sterilized after 14 days. Mice sacrificed after longer intervals (60 to 120 days) showed a lower incidence of positive organ cultures than mice autopsied after 4 to 13 days; 84% of these animals were sterilized. The difference found in the number of mice sterilized with the various sulfonamides tested are not considered to be statistically significant.

(*d*) *Activity and Blood Concentration.* In order to relate the therapeutic results obtained with the concentrations reached in the blood, the absorption following single oral administration of the drugs was determined. The drugs were suspended in 1 cc. of a 5% gum acacia solution and administered to a group of 5 to 7 mice. Mice under ether anesthesia were bled from the external jugular vein at various intervals after administration. The free and conjugated sulfonamide content in the blood was determined according to Bratton and Marshall.[2] The results obtained show that in the therapeutic dose ranges used, sulfadiazine results in a higher and more prolonged blood concentration than the other sulfonamides tested (Table 6). The results on absorption correspond closely to those reported by Schmidt and Sesler.[16]

TABLE 6.—ABSORPTION OF SULFONAMIDES AFTER SINGLE ORAL ADMINISTRATION

Drug	Dose mg. per 20gm. mouse	No. of mice	Blood concentration (total) in mg. % after hours						
			¼	1½	2½	3½	4½	6	7-8
Sulfanilamide	0.5	5	2.0	1.5	0.8	0.8	0.5		
	1.0	13	2.5	2.0	1.5	0.7	0.3	0.5	Tr.
	2.5	18	7.0	5.0	4.0	2.8	1.2	0.5	
	5.0	8	9.5	10.0	5.0	4.5	3.5	2.0	0.5
Sulfapyridine	0.5	4	4.0	2.0	1.0	0.25			
	1.0	4	4.5	4.0	2.0	3.5			
	2.5	11	5.7	7.0	5.7	5.0	4.5	3.8	
	5.0	9	9.0	12.0	9.0	9.0	8.0	5.5	3.0
Sulfathiazole	0.5	13	1.75	0.5	0.4	0.5	Tr.		
	1.0	5	4.0	1.5	0.5	0.5	Tr.		
	2.5	18	7.5	3.0	1.4	1.0	0.5		
	5.0	6	11.0	9.0	7.0	2.5	2.5	2.5	
Sulfadiazine	0.5	13	5.5	6.0	4.3	5.1	5.5		
	1.0	8	8.5	8.0	8.2	7.5			
	2.5	6	11.0	11.0	8.0	8.0	8.0	7.0	
	5.0	14	15.0	18.0	10.0	10.0	12.0	..	10.0

Discussion. The experiments described in this paper show that sulfonamides have a very definite activity on the *Staph. aureus* infection, in the following order: sulfanilamide < sulfapyridine < sulfathiazole < sulfadiazine. These results are in agreement with those of Barlow and Homburger,[1] and Rake and McKee,[14] who found a better activity for sulfathiazole than for sulfapyridine. The effective doses reported here gave (50%) protection against the lethal effect of the infection and brought about complete sterilization in the majority of survivors, as shown by autopsies and organ cultures.

The lowered resistance caused by the use of mucin as an aid for infection was found to decrease also the tolerance of mice to the drug. This explains the phenomenon of the unsatisfactory activity of high doses (10 to 20 mg.) if given repeatedly. Less favorable results of other investigators who used such dosages might be due to this inter-

ference of toxicity with the therapeutic effect. These difficulties have been overcome by the use of single treatment which presented other advantages too. The use of repeated treatment tended to overdose the drug and made the evaluation of the minimal active dose less reliable than that of 1 single treatment. This point is illustrated by Table 7.

TABLE 7.—AVERAGE ACTIVE DOSES OF SULFONAMIDES IN THE S. AUREUS INFECTION OF MICE
(Oral doses in gm./kg.)

Drug	Single treatment (A)	Repeated treatment		Ratio C/A
		Single dose (B)	Total dose (C)	
Sulfanilamide	..	0.250	1.750	
Sulfapyridine	0.375	0.075	0.525	1.4
Sulfathiazole	0.250	0.050	0.350	1.4
Sulfadiazine	0.050	0.025	0.175	3.5

It is evident that in the case of sulfapyridine and sulfathiazole the effective doses for single treatment correspond closely to the total required for repeated treatment with small doses. In the case of treatment with the more active sulfadiazine, the minimal active dose for repeated treatment is 3.5 times higher than required for single treatment. We should like to point out that lower doses given repeatedly, such as 0.0125 and 0.005 gm./kg., were inactive, even though the total amount given exceeded the effective dose by single treatment (0.05 gm./kg.). This would indicate that in order to obtain protection, a sufficiently high initial dose is necessary for the repeated treatment. Altogether, it seems that the treatment with single doses, besides its technical advantages, gives simpler and more clear-cut results.

It is probably not coincidental that sulfadiazine, which showed the highest activity, was better absorbed and gave a blood level of longer duration than the other drugs. No relationship could be found, however, between activity and blood concentration of sulfanilamide, sulfathiazole and sulfapyridine. In fact, the less active sulfapyridine was found to be better absorbed than sulfathiazole.

Summary. 1. The virulence of intra-abdominally injected staphylococci for mice and the influence of mucin on this infection was studied. A method of infection is described which was found suitable for routine determinations of chemotherapeutic activity.

2. The evaluation of sulfonamides administered orally showed that sulfadiazine is about 5 times more active than sulfathiazole. Sulfathiazole is about 1½ times more active than sulfapyridine. Sulfanilamide itself showed a low antistaphylococcal activity.

3. Sulfadiazine, sulfapyridine and sulfathiazole were active even if only 1 single treatment was given shortly before intra-abdominal infection. This mode of administration gave particularly clear-cut results.

4. Autopsies and organ cultures of treated mice showed complete sterilization in the majority of survivors after 14 days.

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PERSISTENCE OF PNEUMOCOCCI IN SULFONAMIDE TREATED CASES OF PNEUMONIA

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In a series of papers beginning in 1938 Frisch[2–4] has described the morphologic features and some of the quantitative aspects of the pneumococci found in stained smears of sputum from cases of pneumonia. He has also described the changes which result from treatment with specific antiserums and with sulfonamide drugs and has indicated their prognostic significance as well as their importance in the control of therapy. The studies which are reported, in part, in this paper were undertaken during the fall and winter of 1941–1942 for the purpose of determining the changes in the bacterial flora of the sputum and pharynx in cases of pneumococcal pneumonia during and after sulfonamide therapy.* An attempt was made to quantitate

* The Senior Author, having been called to military service before this work was completed, it was not possible to complete the work until now. Nevertheless, as the material is still timely, we believe that it represents a useful contribution.

roughly these changes, not only in the pneumococci but also in the relative numbers of the other common respiratory pathogens. In addition to direct morphologic studies similar to those carried out by Frisch, cultural methods were applied to sputum and throat swabbings, and mouse inoculation of sputums and throat cultures were used in each instance.

The present report deals with the results of these studies as they pertain to the persistence, during and after treatment with sulfonamides, of the pneumococci originally present, the appearance of additional types of pneumococci and the fate of these new strains. Earlier studies on the persistence of pneumococci in cases of pneumonia have been reviewed by Finland[1a] and by Harris[6] and the latter reported similar studies in patients treated with sulfapyridine and sulfathiazole. The data bearing on the significance of the finding of various types of pneumococci in patients with pneumonia are reviewed elsewhere.[1b]

Materials and Methods. *Selection of Cases.* The patients chosen for this study were all adults admitted to the medical wards at the Boston City Hospital between the end of September 1941 and the middle of April 1942. They ranged in age between 15 and 64 years and 8 of them were over 50. All of them were acutely ill with pneumonia and had fever, cough and sputum at the time of the first examination and pneumococci were identified in the sputum at that time. There was definite lobar pneumonia by physical examination and by Roentgen ray in all but 5 of the cases. In these 5 cases, there was atypical consolidation that was bilateral, but in 2 of them there was lobar consolidation of 1 lobe in addition. There were 43 patients in all and 3 of them were observed in 2 attacks.

Sulfonamide Therapy. Each of the patients was treated with sulfonamide drugs. Sulfathiazole was used alone in 35 cases, sulfadiazine alone in 4 cases and both of these drugs were used in succession in 6 cases. One of the 3 patients who was observed during 2 attacks received no sulfonamide during the second attack. Treatment was begun in these patients between the 1st and the 8th day after the onset of symptoms of pneumonia. In 31 instances treatment was begun on or before the 3rd day. In 9 cases it was begun on the 4th or 5th day. The average duration of the disease at the time when the treatment was begun was 2.8 days. The usual dosage of sulfonamides was used, namely, 4 gm. for the initial dose followed by 1 gm. every 4 hours. Treatment was continued for 3 days or less in 4 cases, for 4 to 6 days in 18 cases, 7 to 10 days in 17 cases and 15 or more days in 6 cases. The average duration of treatment was 7.6 days. The average dose was 47 gm., about one-half of the patients receiving between 30 and 50 gm. The average blood sulfathiazole level during therapy in 80% of the cases was between 3 and 7 mg. per 100 cc. of the free drug. In 5 instances, high levels were associated with vomiting and nitrogen retention. Specific antipneumococcus serums were used in 3 cases (Nos. 24, 27 and 28).

*Bacteriologic Studies.** Blood cultures were made before treatment in every instance and at frequent intervals after treatment when indicated. Positive cultures were obtained in 8 of the patients, including 4 of Type 1, 3 of Type 7 and 1 of Type 4 pneumococcus.

Sputums were subjected to the following studies: (1) Direct examination for pneumococci with specific antipneumococcus serums by the Neufeld method. (2) Gram stain preparation. (3) Wright stain preparation examined by the method of Frisch. (4) The sputum was homogenized and a 2 mm. loopful streaked thoroughly on the surface of a blood agar plate containing

* Para-aminobenzoic acid, 5 mg. per 100 cc. was incorporated in all media used in this study.

10% defibrinated horse blood. Characteristic colonies were picked and identified and a rough estimation was made of the relative numbers of the different kinds of organisms. (5) Some of the sputum was also inoculated into mice and the peritoneal exudate was examined at suitable intervals by the Neufeld method and cultures of the heart's blood were made and the pneumococci typed when the mouse died or was sacrificed.

Throat cultures were made in some instances at the same time as the sputum and in every instance where sputum was not obtainable. A cotton swab was rubbed against both fauces and against the posterior pharyngeal wall and placed into a tube of nutrient broth containing 1% defibrinated rabbit blood. Some of the broth was mixed thoroughly and streaked directly on the surface of a blood agar plate. The broth was allowed to incubate for 4 to 8 hours until a uniform growth appeared. At that time some of the culture was examined by the Neufeld method and a portion was inoculated, on blood agar plates and intraperitoneally in mice and the peritoneal exudate of the latter examined by the Neufeld method at suitable intervals. The heart's blood of such mice was also cultured when the animals died or were sacrificed.

The Neufeld preparation made directly from the sputum was studied both for the various types of pneumococci and for the numbers of each type. In the Gram and Wright stain preparations similar counts were made of characteristic lancet-shaped diplococci. In the Wright stain preparation observations were also made of clumping and phagocytosis of diplococci and also of reticulation as noted by Frisch.[2]

The direct surface cultures were observed for the relative numbers of the common respiratory pathogens, namely, pneumococci, hemolytic and green-producing streptococci, *Staphylococcus aureus* and *Hemophilus influenzæ*. These various organisms other than the pneumococci were identified only by their colony characteristics and their morphologic appearance in stain smears and the staphylococci were also tested for coagulase activity.

The throat cultures were studied mainly with the idea of observing the persistence of pneumococci. The pneumococci were identified by subjecting the direct cultures, the peritoneal exudate of mice or the characteristic colonies picked from the blood agar plate to the action of type-specific antiserums (Neufeld). Doubtful colonies were subcultured and tested for bile solubility. Sensitivity of the strains to sulfonamides was tested by essentially the same method as was used in a previous study in this laboratory.[7]

Sputums and throat cultures were thus obtained before the first dose of sulfonamide and at suitable intervals during and after treatment. A total of 244 sputums were studied in the 46 cases, and, in addition, 90 throat cultures were made in 35 of the cases making an average of more than 7 specimens studied in each attack. The average hospital stay for each attack was 18 days, but the patients were asked to return after discharge from the hospital for follow-up studies. The last sputum or throat culture was made in 15 cases on or before the 15th day; in 14 cases between the 15th and 30th day; in 14 cases between the 31st and 60th day; 3 cases were observed for longer periods. The average time between the first and the last observation was 31 days. This period is exclusive of the interval between the recurrences in 3 of the patients.

Results. In this paper, only the results of the findings of pneumococci in this series of cases are being presented. The types of pneumococci found before treatment was begun and data concerning the persistence of these pneumococci are given in Table 1. In addition, the relevant findings concerning the pneumonia and the sulfonamide therapy are summarized for each case in this table. A total of 51 strains were isolated before treatment in the 46 attacks which occurred in the 43 patients studied. Of these, 34 strains were of the types commonly associated with primary lobar pneumonia, namely, Types 1,

TABLE 1.—FATE OF PNEUMOCOCCI FOUND IN SPUTUM AT THE TIME SULFONAMIDE THERAPY WAS STARTED

Case No.	B.C.	Lobes	Chemotherapy: Drug	Begun	Grams	Days	Pneumococci: Type	Days	Day last test	Complications, clinical response, etc.
1	0	Ll	T4	2	29	6	8	10	10	C1
2	0	Rl	T7 D8	3	35	6	1	48	48	C2
							3	1		
3	0	Ll	T13	2	16	2½	1	2	12	C1
4	0	B	T3	2	32	4½	11	3	6	C1; chronic bronchitis
5	0	Ll	T4	1	35	8	27	1	41	C2; chronic bronchitis
							24	41*		
6	0	Ll	T6	5	25	3½	25	7	179	C2; pn. (?) 9 yrs. before
6R	0	Rm	..	..	..	..	19	10	10	C1; recurrence after 5½ mos.
7	0	Ll	T7	2	25	3	8	118	118	C1; bronchiectasis; sinusitis
8	0	Ruml	T6	5	57	10	2	2	9	D16; alc.; uremia
9	1	Ll	T4	7	54	8	1	2	23	C1; alc.; sinusitis
10	0	Ll	T5	3	50	8	1	3	177	C2; frequent colds
							6	1		
11	0	Ru	T5	2	25	3½	2	2	77	C2; pn. several times
11R	0	Rl	T3	2	36	5½	12	3	11	C1; recurrence after 2 mos.
							8	1		? bronchiectasis
12	0	Ll	T4	3	45	7	8	19	19	L2-5; pn. (14) and pn. (2) 4 and 2 yrs. before; chronic bronchitis
13	0	Rml	T3	4	44	7	7	4	8	C2; alc.
14	7	Ll	T6 D	10	54	8	7	3	10	D10; meningitis (7); sinusitis, Staph. aureus and Strep. hem.
15	0	Rml	T5	3	32	5	1	11*	11	C2
16	0	Ru	T	2	7	1	2	9	22	L3; pn. (1) 4 yrs. before
17	0	Rm	D9	1	36	6	1	2	8	C2; otitis
18	0	Rul	T3	4	40	6	2	8*	8	C3
19	0	B	D9	6	39	8	3	237*	237	L2-3; chronic bronchitis
19R	0	B	D9	5	28	5	3	196*	196	C1; recurrence after 6 wks.
20	1	Rum	T9	2	43	7	1	1	33	L2-4; pn. (4) 4 yrs. before
21	4	Ru	T12	6	10	1	4	50*	50	C1; relapses—fever 26 days; azotemia
22	0	Rml	T4	1	28	4	14	3	83	C2
23	0	B Ll	T10 D11	1	43	6	3	1	17	C2; oliguria; azotemia; drug fever; chronic bronchitis
24	0	B	T9 D20	4	48	8	9	9	9	D9; Type 9 antiserum 8th day
25	0	Ruml	T4	7	36	5	4	1	10	L1-2; pn. (6) 1 yr. before; alc. D.T.
26	0	Rl	T4	1	42	7	3	2	8	L3
27	0	Llu	T3	1	100	16	29	5	25	L18; post-traumatic; Type 29 antiserum 3rd day; sterile pleural effusion
28	7	Ll	T3	2	98	16	7	5	57	L13; Type 7 antiserum 1st day; alc.; sterile effusion
29	1	Rml	T3 D	3	162	26	1	87*	87	Empyema, rib resection
30	1	Ll	T6	3	87	10	1	1	26	C1; sterile pleural effusion
31	0	R2	T3	5	42	6	7	1	39	C2
32	0	R2	T5	2	25	5	5	36	100	C2; persistent "colds"
33	0	L2	T3	2	33	5	7	1	3	C2; pn. 12 yrs. before
34	0	L2	T5	2	61	10	1	18*	32	C2; pn. 2 yrs. before; sterile pleural effusion
35	0	Ru	D	3	52	8	2	1	54	C2; pn. (7) 3 yrs. before and pn. (1) 1 yr. before; pn. 8 other times; bronchiectasis
							33	2		
36	0	Rml Ll	T5	1	48	8	3	1	16	C1; alc.; chronic bronchitis
37	0	Lul	T11	4	57	9	2	28*	28	C2; chronic bronchitis; sinusitis; pn. 10 yrs. before; otitis
38	0	Rul	T4	1	32	4½	1	8	20	C2; pn. in childhood
39	0	L2	T6	1	30	4½	5	2	7	C2
40	7	Rml	T5 D11	5	121	20	7	29*	34	Empyema; drug fever and rash
41	0	L2	T5	2	44	8	1	3	27	L1-3
42	0	L2	T3	2	47	7	7	21*	21	L2-4
43	0	L2	T4	2	98	18	1	1	13	C2; empyema

ABBREVIATIONS AND EXPLANATIONS: Under "Case No.": R = recurrent infection; B.C. = blood culture; 0 = no growth, numeral = type of pneumococcus found in positive B.C. Under "Lobes": L = left; R = right; u = upper; l = lower; m = middle; B = diffuse bronchopneumonia. Under "Drug": T = sulfathiazole; D = sulfadiazine; the numbers represent the average blood levels of free drug in mg. % to the nearest whole number. Under "Begun": numbers represent days after onset of the disease. "Days" Under "Chemotherapy," "Pneumococci" and "Day Last Test": the numbers represent days after sulfonamide therapy was started, the last of these being the day when the last specimen was obtained. Under "Clinical Response, Etc.": C = crisis; L = lysis; D= died; the number after these letters represent the day after drug therapy was started. pn. = past history of pneumonia, the number in parenthesis being the type when known; Alc. = alcoholism; D.T. = delirium tremens.

* One or more specimens prior to the last one were negative for the same type.

2, 5, 7 and 8; 6 strains were Type 3; 11 strains were either Type 6 or of the so-called "higher" types.

There were 5 cases in which 2 types were isolated before treatment was begun: Types 1 and 3 were found in Case 2, Types 27 and 24 in Case 5, Types 1 and 6 in Case 10, Types 2 and 33 in Case 35 and Types 12 and 8 during the recurrence in Case 11. Except in Case 5, therefore, one of the common types was found in conjunction with one of the "higher" types or with one of the types commonly found in carriers (namely, Types 3 and 6). In 1 of the cases observed during 2 attacks the Type 3 pneumococcus was found before treatment in each attack.

Persistence of the Pneumococci Found Before Treatment. Of the 51 strains, 36 could no longer be found in the last sputum or throat culture. The last specimen in which these 36 strains were found was obtained on the 1st day of treatment in 13 instances on the 2nd or 3rd day in 14, on the 4th to 7th day in 4 and on the 8th day or later in the remaining 5 strains. In 2 of the latter, several specimens failed to yield pneumococci but these reappeared toward the end of the period of observation. The average time elapsed from the onset of treatment to the time when these strains were last found was 4.7 days, and 27 of these 36 strains of pneumococci were last found on or before the 3rd day. Thirty of these 36 strains (83.3%) had disappeared from sputum or throat cultures before the course of sulfonamide therapy was completed. The average period of observation of these cases was 41 days.

The 15 remaining strains* persisted throughout the period of observation which averaged 60 days. The last sputum or throat culture was studied during the 2nd week in 4 cases, during the 3rd or 4th week in 4 others, during the 2nd month in 4 cases and from 5 to 8 months after treatment in the remaining 3 cases. In 9 instances these strains were found intermittently throughout the period of observation, that is, each of them could not be found in one or more specimens studied before the last one was obtained. Pneumococci tended to persist when treatment was begun after the 2nd day of illness although some cleared rapidly even in cases treated after 7 days.

Appearance of Additional Strains of Pneumococci During or After Therapy. In addition to the strains of pneumococci identified before treatment was begun, pneumococci of different types appeared after treatment was begun in 17 patients including Case 19 in which a second and different type appeared during each of 2 attacks. The types of these strains and the time of their first and last appearance are shown in Table 2. It is of interest that only 1 of these new strains was of any of the common types, other than Type 3, which are usually associated with primary pneumococcal pneumonia. The isolated instance was that of a Type 1 pneumococcus, which was found only in the last specimen studied in Case 28. A Type 4 pneumococcus was found on the 2nd day of therapy of the recurrence in Case 19. Of the

* The Type 3 pneumococcus in Case 19 is counted twice since it was found before treatment in each of 2 attacks.

remainder, 4 were Type 3 strains and 20 were of the "higher" types. In Case 5 there were 4 types identified in addition to the 2 types which were originally present before sulfonamide therapy was begun and in Case 28, 4 new types of pneumococci made their appearance after treatment was begun, in addition to the Type 7 which was originally present. In 3 other cases, 2 new types were first found after the onset of therapy and in the remaining cases only 1 new strain was identified in addition to those originally identified before the onset of therapy.

TABLE 2.—APPEARANCE AND FATE OF PNEUMOCOCCI FOUND FOR THE FIRST TIME AFTER SULFONAMIDE THERAPY WAS STARTED

Case No.	Sulfonamide treatment (days)	Pneumococcus type	Days after chemotherapy begun: First appeared*	Last found	Agglutinins demonstrated
1	6	17	5	5	None
2	6	18A	48	48	4
5	8	13	2	13	1
		20	4	41†	None
		3	4	8	1
		19	25	41	None
7	3	17	118	118	None
10	8	14	149	177	None
		15	149	177	None
16	1	9	22	22	4
19	8	29	3	4	1
19R	5	4	2	2	21
22	4	28	32	83	None
		24	54	54	None
26	7	15	4	4	40
28	16	21	10	10	None
		3	43	43	None
		23	43	43	None
		1	57	57	None
29	26	27	87	87	35
32	5	28	20	100	None
34	10	3	2	2	None
35	8	24	14	54	None
41	8	20	8	27	None
43	18	3	2	2	None
		13	3	3	None

For relevant data concerning these cases see Table 1. Pneumococcus type present when treatment of a recurrent infection was started are not listed here but are given in the previous table. Agglutinins listed are for the corresponding types; the numbers represent days after treatment when antibodies were first demonstrated.

* 14 of these 26 strains were first found while the patient was still receiving sulfonamides.

† Several sputums were interspersed through the course of the illness from which this type was not recovered.

Altogether, therefore, there were 26 additional strains found in these 17 patients; 14 of these strains appeared in 9 patients while sulfonamide therapy was still being given. The remaining 12 strains were first observed in 8 cases after the sulfonamide therapy had already been discontinued. Nine of the former strains and 7 of the latter were found only in a single sputum or throat culture and in 5 instances that was the last specimen studied. Of the 10 strains which were found more than once, 3 persisted for only 1 to 11 days and the remain-

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ing 7 were still present in the last specimen studied which was obtained from 16 to 80 days after these strains first appeared.

A summary of the occurrence of the different types of pneumococci both those present before treatment and those which made their first appearance after treatment was begun, is given in Table 3. A total of 77 strains of pneumococci were identified in the 46 cases studied. A single type of pneumococcus was obtained during 28 of these attacks; 2 different types were obtained in 11 cases; 3 types in 4 cases and 4, 5 and 6 types were obtained in 1 case each.

TABLE 3.—DISTRIBUTION OF TYPES ACCORDING TO THEIR APPEARANCE AND FATE IN RELATION TO SULFONAMIDE THERAPY

Types	Number of strains present before sulfonamide therapy		Number of strains which appeared after sulfonamides were begun		Total
	Absent from last specimen	Present in last specimen	Absent from last specimen	Present in last specimen	
1, 2, 5, 7, 8	24	10	1	1	36
3	4	2	4	0	10
Others	8	3	8	12	31
All	36*	15	13†	13‡	77

* 30 of these strains were already absent from the sputum or throat culture before sulfonamide therapy was ended and the other 6 were still present after chemotherapy had been discontinued.

† 9 of these strains disappeared during sulfonamide therapy and 4 were still present after chemotherapy was stopped.

‡ 4 of these strains, including a Type 1 strain, were found only in the last specimen.

Recognition of Pneumococci During and After Sulfonamide Therapy. Throughout this study there was no difficulty in recognizing pneumococci and identifying their types irrespective of whether they were found before treatment was begun, during therapy or after the sulfonamides had been discontinued. In almost every instance in which sputum was available the pneumococcus types were identified directly in the sputum by the Neufeld method. In every instance characteristic colonies were observed on the surface of blood agar plates and the organisms preserved their morphologic and cultural characteristics and their virulence for mice. All of the strains present in the peritoneal exudate or in the heart's blood of mice were easily identified by the Neufeld method.

Clinical Response to Treatment. There were 3 deaths in this series. In 1 of these cases (No. 8) blood cultures were negative; death was associated with uremia, and the Type 2 pneumococcus originally present in the sputum could not be found after the first 2 days of sulfonamide therapy. In Case 14, the Type 7 pneumococcus was obtained from blood cultures taken before and 12 hours after treatment was begun, but not thereafter; it was found in the sputum only during the first 3 days but it was recovered from the purulent meningeal exudate at autopsy. In Case 24, blood cultures were negative but the Type 9 pneumococcus persisted in the sputum up to the day of death. In the latter case, specific antipneumococcus serum was given on the day before death.

Among the recovered cases, 31 were essentially afebrile and free of acute symptoms within 48 hours after the first dose of sulfonamide, while in 8 others some fever and acute symptoms persisted for 3 to 5 days. In 4 cases, persistent fever was associated with pleural effusions, 2 of which were sterile and the other 2 infected. In 1 other case of empyema and in 2 additional cases with sterile pleural effusions fever recurred after an apparently critical improvement associated with drop in temperature to normal which occurred within 48 hours of the beginning of treatment. Of the 36 strains present before treatment in the 31 cases in which recovery took place within 48 hours, 22 (61%) persisted only for 3 days or less, whereas 5 of the 8 strains originally found in the patients who had fever for 3 to 5 days were found for 8 days or longer after treatment was begun. The cases with complications will be considered later.

Bacteriemic Cases. There were 8 patients in whom positive blood cultures were obtained before sulfonamide therapy was started. In 5 cases pneumococci of the type found in the blood could not be found in the sputum or throat cultures after the 3rd day. In the other 3 cases the same type was found in the sputum or throat cultures throughout most or all of the period of observation; 2 of the latter cases had empyema and the third (Case 21) had azotemia during sulfonamide therapy and a relapse of fever after 26 days.

Complications of the Pneumonia and Their Effect on the Persistence of Pneumococci. Empyema occurred as a complication in 3 cases. In 1 of them, Case 29, Type 1 pneumococci were found intermittently throughout the 87 days of observation and a Type 27 pneumococcus appeared for the first time in the last sputum examined. In a second case, No. 40, the Type 7 pneumococcus was found in all but 1 of the specimens obtained up to the 29th day but not thereafter. In Case 43, the Type 1 pneumococcus was found in the sputum only on the 1st day of treatment although it was recovered during the following 12 days from cultures of the pleural fluid. Types 3 and 13 pneumococci were each found on 1 occasion on the 2nd and 3rd days respectively. In Case 14, meningitis occurred terminally and Type 7 pneumococci were obtained from cultures of the meninges but this organism could not be obtained from the sputum later than 36 hours after sulfonamide therapy was started. Blood cultures in this case were positive before treatment was begun and 12 hours after the first dose but were negative thereafter. Bilateral catarrhal otitis media occurred in Case 17 and in Case 37, but pneumococci persisted in the sputum only in the latter. Extension of the pulmonary process occurred early in the course of sulfonamide therapy in Case 25 and Case 27 but pneumococci could not be recovered after the 1st day of treatment in the former and after the 5th day in the latter.

Previous History of Pneumonia. Such a history was obtained from the patient or from the hospital records in 16 cases. In 11 of them there was no information concerning the bacteriology of the previous attacks. In 5 of the patients, however, the previous attacks were associated with type-specific pneumococci and they included 2 patients

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in which there were 2 previous attacks of pneumococcal pneumonia. In each of these 7 previous attacks the type of pneumococcus was different from the one found in the present series. Of the 3 cases which were observed during 2 attacks in the course of this study, 1, Case 19, had a Type 3 pneumococcus before treatment on each occasion, but Type 29 was found in addition on the 3rd day of the first attack, and Type 4 was obtained on the 2nd day of the recurrence which began after an interval of 6 weeks. The interval between the initial observed attack and the recurrence was 5½ months in Case 6 and 2 months in Case 11. In these 2 patients different types of pneumococci were obtained in each of the attacks. The pneumococci found in this group of cases behaved in about the same manner as in the other cases. More than half of the 21 strains from these cases could be found for only 1 to 3 days while the others persisted for varying periods.

Effect of Chronic Respiratory Infections. A history of chronic bronchitis was obtained in 11 cases, and 3 other patients had chronic or frequently recurring infections of the upper respiratory tract. In this group of cases there was considerable variation in the persistence of pneumococci. In some of them the pneumococci found in the sputum before treatment cleared rapidly, in others they persisted for a variable period and then could no longer be found, and there were still others in which the pneumococci were recovered throughout the period of observation. In 7 of these cases there were multiple types of pneumococci. The new types which appeared during or after sulfonamide therapy showed similar variations with respect to the time during which they could be recovered.

Immunologic Findings. Antibodies were demonstrated for 1 of the types of pneumococci originally found in the sputum in all but 2 cases, namely Case 19 in which Type 3 was found and Case 32 in which there was a Type 5 pneumococcus. In only 1 of the cases in which 2 or more types were found before treatment were agglutinins found against more than 1 of these types; in Case 2 agglutinins for the Type 3 pneumococcus were found in the serum obtained before treatment and Type 1 antibodies appeared later. In the remaining cases antibodies developed against only one of the types originally found in the sputum. In Case 5 agglutinins developed for Type 27 but not for Type 24; in Case 10 antibodies were demonstrated for Type 1 but not for Type 6. In Case 11 agglutinins for Type 2 pneumococci developed during the first attack but none could be demonstrated either for the Type 8 or the Type 12 pneumococci which were found before the treatment of the second attack and in Case 35 antibodies developed during the course of treatment against Type 2 but none could be found against Type 33 in any of the serums tested.

As to the types which appeared after treatment was begun (see Table 2) antibodies for them could not be demonstrated in any of the serums in most instances. Agglutinins were found, however, against 8 of the strains, but in 6 instances these antibodies were already present in blood which was obtained before the homologous type first made its appearance.

Susceptibility of Strains to Sulfonamides. A total of 76 pure cultures from isolated colonies of 43 strains of pneumococci obtained from 26 patients were tested for their sensitivity and for their susceptibility to the action of sulfathiazole and sulfadiazine. In 22 instances the strain was tested from only a single isolation which usually was the one made from sputum obtained before treatment was started. The remaining 21 strains were each freshly isolated on 2 to 6 different occasions during and after sulfonamide therapy. The first isolation of each strain was usually made before treatment was begun. The interval between the first and last isolations of the 21 strains of which there were multiple cultures varied from 2 to 55 days and averaged 14 days. The cultures were tested in large batches and all of those obtained from the same case were tested at the same time.

The growth of all of the cultures of the various strains was inhibited by lower concentrations of sulfathiazole than of sulfadiazine in parallel tests. The inoculum was approximately 10,000 diplococci per cc. in each instance. Growth in rabbit blood broth was completely inhibited by sulfathiazole in concentration of 5 mg. per 100 cc. in 18 of the cultures and in 2.5 mg. in 53 cultures. In 3 instances, there was complete inhibition of growth with 1 mg. per 100 cc. and 2 others required 10 mg. to bring about this result. For sulfadiazine, a concentration of 10 mg. per 100 cc. was required for complete or nearly complete inhibition of 6 strains; 5 mg. for 52 strains; 2.5 mg. for 17 strains; 1 mg. for 1 of the strains. These concentrations were sufficient to prevent visible growth from occurring in the broth cultures and only occasional colonies grew out in some of them when transfers were made after 48 hours to a blood agar plate containing para-aminobenzoic acid. Although these differences were noted among the various strains, no significant differences could be demonstrated in the resistance of any one strain which was isolated on more than one occasion.

Discussion. After sulfapyridine and the other effective sulfanilamide derivatives came into general use, the impression became prevalent that it is difficult or impossible to culture and to type pneumococci from cases of pneumonia which are under treatment with these drugs. Part of the purpose of the present study was to determine whether this was due to the actual disappearance of the pneumococci during treatment or whether it was necessary to use more extensive cultural methods or mouse inoculation in order to find them. In general, it was found that when pneumococci were present, they usually could be identified in the sputum even during the course of sulfonamide therapy. Only in occasional specimens were pneumococci obtained from cultures or after mouse inoculation when they could not be found by careful search of the sputum in a Neufeld preparation. In cases which responded favorably, to be sure, pneumococci were often present in very small numbers during the sulfonamide therapy and some of the organisms showed the morphologic changes described by Frisch.[2]

The data presented indicate first of all that there are considerable variations in the persistence of pneumococci in cases of pneumonia treated with sulfonamides just as had previously been shown in cases

not treated with these drugs. In a large proportion of sulfonamide treated cases, however, it was not possible to find the pneumococci after the 2nd day of adequate therapy. As far as could be judged from the small amount of data available, the pneumococci tended to persist longer in those cases in which the clinical response to treatment was delayed than in those in which the fever and the acute symptoms subsided in less than 48 hours after the sulfonamides were started.

In general, pneumococci tended to persist longer in cases with purulent complications, and in those in which there was a history of chronic respiratory infections. In the latter cases additional types were recovered more frequently during and after sulfonamide therapy. It is possible that minor unrecognized complications such as small pulmonary abscesses or persistent asymptomatic bronchitis may have been present to account for the persistence of pneumococci in some of the other cases.

Presumably, the new types which appeared for the first time after sulfonamide treatment was started, particularly those found early in the course of therapy, were also present before that time. Failure to find them may have been due to their presence in relatively small numbers, or to failures of the methods used. As to the strains which made their appearance later, it is not possible to state whether they were originally present or were newly acquired. The fact that some of the strains of pneumococci were found only intermittently even after treatment was stopped would tend to indicate that most of the new strains were probably present earlier.

The persistence of pneumococci was apparently not related to the failure of the patient to develop homologous antibodies. In the first place, almost all of the patients developed antibodies against those of their homologous strains which could be presumed to be the causative agents of their disease, irrespective of whether those strains persisted or disappeared rapidly. Secondly, in the case of some of the strains which made their appearance after treatment was begun antibodies for them were often detected in serums which were obtained before the time when the corresponding strains were first isolated. It is probably justifiable to assume that these antibodies were the results of previous infections with those strains, the infections being either inapparent or manifest but mild. Almost all of the newly acquired strains were of the "higher" types against which antibodies can only rarely be demonstrated in human cases by the agglutination method.[15]

In the present cases, full therapeutic doses of the sulfonamide drugs were used. While there is no way of judging whether the blood levels obtained were optimal, they seemed to be therapeutically effective. It is not possible, however, to draw definite conclusions from the results of the *in vitro* tests for the susceptibility of the strains. In these tests large numbers of pneumococci were used in a medium which is known to contain inhibiting substances. Other sulfonamide inhibitors are known to occur in the patients' tissues and some of them are present in significant quantities in purulent foci.

It was expected that some of the strains which persisted in spite of

prolonged treatment would become resistant to the action of the sulfonamides. The development of such resistance has been demonstrated in occasional cases of pneumonia,[2c,7] but it seems to be far less frequent than one would suppose. It is of interest that none of the strains tested in the present cases became resistant during treatment, although some of them were readily obtained from sputum and throat cultures after prolonged sulfonamide therapy. It is the practice of some physicians to reduce the dose of sulfonamide and to continue treatment with the smaller doses for several days after the fever subsides. It is possible that under such circumstances or under the régime of continuous small dosage, which is recommended for the prophylaxis of respiratory infections and of rheumatic fever, resistant strains might develop more readily.

The effect of penicillin therapy on the persistence of pneumococci is being studied in this laboratory. With this therapy, too, pneumococci have been found to persist in many cases after doses which are sufficient to bring about rapid clinical improvement.[5]

Summary and Conclusions. The persistence of pneumococci in sulfonamide treated cases of pneumonia was studied by the examination of sputum and throat cultures obtained in 43 patients before and at intervals during and after treatment with sulfathiazole or sulfadiazine. Three of the patients were studied during 2 attacks of pneumonia. Considerable variations were found in the persistence of pneumococci in these cases. Of the strains of pneumococci found before the sulfonamide therapy was started, about 30% persisted throughout the period of observation or were obtained intermittently during this time. Three-fourths of the remaining strains could no longer be found after the 3rd day of treatment.

New types of pneumococci which were not found in the pretreatment cultures appeared in the specimens studied during or after sulfonamide therapy in a considerable proportion of the cases. Most of the strains which first appeared during sulfonamide therapy could no longer be found after that treatment was completed.

Multiple types of pneumococci were found more frequently in patients with a history of chronic respiratory infections. In these cases and in those with purulent complications of the pneumonia there was a greater tendency for the pneumococci to persist than in uncomplicated cases.

The persistence of pneumococci was not related to the failure of the patient to develop antibodies for the homologous types.

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A CLINICAL STUDY OF SENSITIVITY TO SULFATHIAZOLE

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The therapeutic administration of the sulfonamide drugs may lead to untoward reactions of various types, which, while the individual manifestations vary widely may be divided into three groups on the basis of their pathogenesis: (1) direct toxic effects such as the vomiting induced by sulfapyridine and sulfathiazole, and the cyanosis induced by sulfanilamide; (2) mechanical effects due to precipitation of the drug or its acetyl derivative in the urinary passages; (3) allergic reactions or reactions of hypersensitivity such as drug fever and eruption.

While most of the individual reactions can be assigned to one or another of these groups, some, such as hepatitis and anemia, cannot be easily classified. The present study was undertaken in order to obtain information as to the time of appearance of certain of the allergic reactions to the drugs, as well as of the incidence and time of onset of allergic reactions when the drug was readministered after being withheld for an interval.

Estimates of the incidence of allergic response to sulfathiazole on initial administration vary from 2 to 10%. Lyons and Balberor[3] were the first to point out that many patients who had received an initial course of sulfonamide with impunity, responded to a second administration by the prompt development of drug fever. This occurred in 36% of their 53 cases. Talbot and Adcock[4] reported that of 37 patients given sulfadiazine in 2 courses, 16.2% had drug fever on the second course, while only 8.1% had shown this symptom on the first exhibition of drug. Dowling and Lepper[1] reported an incidence of 16.7% of drug fever with a second course of sulfathiazole in 53 cases but did not state the incidence on the first administration in this same group.

Procedure. To obtain data on incidence of allergic reaction on primary administration of the drug, the charts of 472 patients, who had been given sulfathiazole while in the hospital, were examined. Fever without other assignable cause which disappeared on withdrawal of the drug, cutaneous eruptions including erythema nodosum, and conjunctivitis, which were related in a similar way to ingestion of drug, were taken as allergic reactions. One case of nephrosis, in which the possibility of mechanical obstruction to urine flow could be definitely excluded, is included. Cases of gross or microscopic hematuria, anemia, and leukocytosis were not included as allergic phenomena because of uncertainty as to the type of reaction they represent. In order to obtain data on response to readministration of drug, 528 additional charts were examined, a total of 1000.

Primary Administration. Table 1 presents all of the untoward effects of the drug in 472 cases. Of this group, 110 patients exhibited some form of reaction; 46, approximately one-half of these 110 patients, had definite sensitivity reactions; of the 71 patients who had reactions other than nausea and vomiting, 65% had allergic responses. Drug fever occurred in practically all cases showing any type of sensitivity reaction. Therefore, we are using it as an index of allergic response in order to simplify the presentation of data.

TABLE 1.—UNTOWARD REACTIONS ON FIRST ADMINISTRATION OF SULFATHIAZOLE

	No. cases	%
Drug fever	38	8.05
Skin rash	14	2.97
Erythema nodosum	1	0.21
Conjunctivitis	6	1.28
Nephrosis	1	0.21
"Plugging" of urinary tract	2	0.42
Renal colic	2	0.42
Oliguria	15	3.18
Nausea and vomiting	71	15.00
Delirium	2	0.42
Microscopic hematuria	14	2.97
Gross hematuria	4	0.85
Anemia	1	0.21
Leukocytosis	3	0.64
Leukopenia	1	0.21
Arthralgia	3	0.64
Soreness balls of feet	1	0.21

In Figure 1, these febrile responses are shown, distributed by day of onset. Since the number of patients receiving the drug diminished rather rapidly when the time of administration exceeded 3 days, percentages rather than absolute numbers are plotted. The absolute numbers are, however, given in Figure 1. It is evident that the peak incidence of drug fever was reached on the 9th day, the curve dropping sharply after that. Too few patients received drug for more than 11 days to justify calculation of percentages. It is noteworthy also that of the whole number of 38 reactions, over half had their onset between the 7th and 10th days, one-third beginning on the 8th or 9th day. The 1 patient who developed drug fever on the 1st day of administration had had sulfanilamide 1 year before, and perhaps should be classified as a cross-sensitivity case. None of the others, as far as could be determined, had had sulfonamide previously.

Readministration. Sulfathiazole was given twice to 103 patients, with an interval of from 2 to 180 days between courses. Detailed data concerning the 22 which had allergic reactions are given in Table 2, and the incidence of reactions on the different courses is summarized in Table 3.

All of the patients who had drug fever on the first administration developed fever on the 1st or 2nd day of readministration of the drug. However, although the great majority of cases once having reacted to the drug develop manifestations of sensitivity when another course of the drug is given, this rule is not absolute. Case 21 had conjunctivitis on the first administration but showed no reaction during a 3-day

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second course. Also Case 20 developed drug fever on the second administration but had no reaction on a third course of 4 days.

In 12 patients who reacted to the second administration of sulfathiazole, but had no reaction on the first course, not 1 developed a reaction before a period of 9 days had elapsed from the time the first course was started. This had previously been noted by Lyons and Balberor.[3]

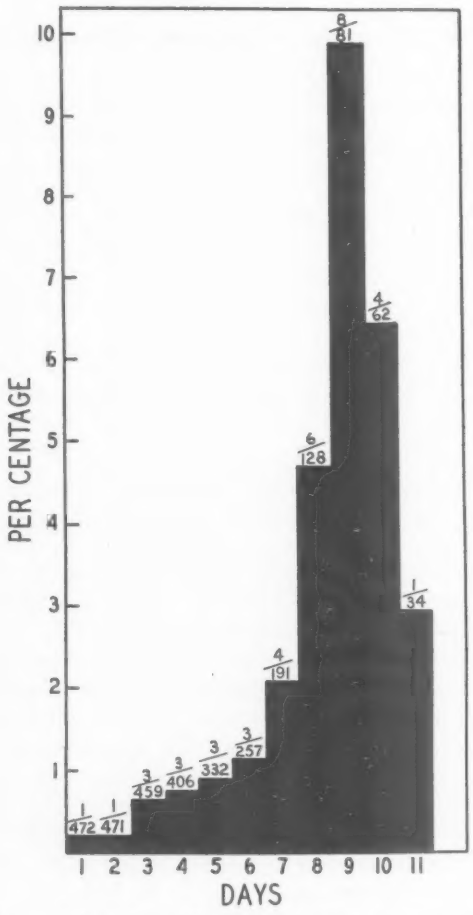

FIG. 1.—Incidence of drug fever distributed by day of onset in 472 cases receiving sulfathiazole for the first time.

We wished to determine what effect the total number of days during which sulfathiazole is administered on both courses might have in relation to development of reactions on the second course. In 12 patients who had drug fever on the second administration and not on the first, the onset of reactions on the second course occurred after from 4 to 15 days of total therapy, with no definite grouping on any individual day. These data suggest that the total time of administration

bears no relation to the time of onset of sensitivity reactions on the second course.

TABLE 2.—READMINISTRATION CASES WITH SENSITIVITY REACTIONS

No.	1st administration				2nd administration					3rd administration				
	Gm.	Days	React.	Day of react.	Interval	Gm.	Days	React.	Day of react.	Interval	Gm.	Days	React.	Day of react.
1	31	8	..	..	5	9	5	F C	2 5					
2	17	3	..	..	7	9	5	F R EN	1 3 3					
3	49	8	..	..	8	4	2	F R	1 1					
4	36	7	..	..	7	9	7	F R	1 6					
5	50	9	F R	9 11	34	2	1	F	1					
6	44	12	F	7	5	10	1	F	1	210	16	3	F	2
7	42	5	F	4	9	3	1	F	1					
8	2	1	F	1	2	3	1	F	1	1	2	1	F	1
9	48	6	F	?	4	12	1	F	2					
10	9	3	..	..	7	8	4	F	2					
11	13	3	..	..	6	6	2	F	2					
12	10	2	..	..	3	28	5	F	?	330	45	8	R C N	7 6
13	52	14	F	?	60	13	3	F	2					
14	7	3	..	..	41	9	6	F	6					
15	64	8	..	..	6	20	3	F	1					
16	7	2	F	5	9	2	1	F	1					
17	19	4	..	..	5	29	9	F	7					
18	79	9	..	..	180	31	6	F	1					
19	31	6	F R C	?	5	1	1	F	1					
20	23	5	..	..	13	45	10	F	10	33	12	4		
21	18	5	C	3	12	10	3							
22	7	4	..	..	3	4	2	F	2					

F = Drug fever. R = Skin rash. C = Conjunctivitis. N = Nephrosis. EN = Erythema nodosum.

TABLE 3.—INCIDENCE OF SENSITIVITY REACTIONS ON READMINISTRATION OF SULFATHIAZOLE

	No. cases	%
Total with no reaction on any course	81	78.6
Reaction first time not second	1	1.0
Reaction second time not first	13	12.6
Reaction on each administration	8	7.8
Reaction on first administration	9	8.8
Reaction on second administration	21	20.4
Total receiving 2 or more courses sulfathiazole	103	100.0

The duration of the first course should be examined in relation to the development of reactions on the second course. The data suggest that the incidence of sensitivity reactions on the second administration is no greater with a prolonged first administration than with a short initial course, but there are too few cases to justify a definite conclusion. However, 4 patients who had received sulfathiazole for 4 days or less on the initial administration without reaction, developed signs of

sensitivity within the first 2 days of the second course. Thus, it is important to note that a short initial course, not accompanied by reaction, may effectively sensitize to subsequent administrations.

All of the patients who had drug fever on an initial course developed fever within the first 2 days the second time the drug was given. Also, 9 out of 12 (75%) cases reacting to the second administration and not the first developed drug fever on the 1st or 2nd day of the second course. Fifteen of 19 (79%) of the cases described by Lyons and Balberor developed drug fever within the first 2 days of the second administration. Thus, the brief time in which drug fever appears in many cases after the beginning of the second course points strongly toward the type of reaction seen in individuals already sensitive to an allergen, since it is not readily conceivable that these patients developed sensitivity *de novo* within 2 days. Cases 14, 17 and 20 developed fever on the 6th, 7th and 10th days after the beginning of the second course. It is possible that these cases were not sensitized by their initial course, and that their reactions developed at the time when they would be expected on a primary administration. If it is assumed that the early reactions on the second course are manifestations of preëxisting sensitivity, it can be stated that 9 of 103 patients (8.8%) given 2 courses of sulfathiazole were sensitized by the initial course without displaying any evidence of sensitivity on the first administration. However, the length of the initial course plus the duration of the interval must equal or exceed 9 days in order that a reaction may occur on the second administration.

From our data we are unable to demonstrate any influence of dosage, either total or daily, on the incidence of reactions. However, we have noted that some individuals when sensitive to sulfathiazole will develop drug fever 30 minutes after 0.5 gm. of the drug, whereas others require 4 to 8 gm. in order to produce signs of sensitivity. Thus, it is probably true that individuals vary in their threshold of sensitivity to sulfathiazole.

Comment. The peak incidence of drug fever on initial administration of sulfathiazole occurs on the 9th day (9.9%), after which the incidence of this reaction declines sharply. Therefore, if a patient has received the drug for 9 days without developing drug fever, the chances that he will have fever subsequent to this on the same administration diminish rapidly.

It has been suggested that the incidence of drug fever on the second administration of sulfathiazole is enhanced by an interval between courses. If the readministration cases that developed fever on the first course are withheld from consideration, then the figures are biased by the removal of the cases which we know would develop sensitivity reactions on the second administration. Therefore, a lower incidence of reactions on subsequent administrations would be expected in this group. However, the incidence of fever in this biased group is higher (12.6%) than that in the cases receiving sulfathiazole for the first time (8.1%). Furthermore, 75% of our sensitivity reactions occurred

within the first 2 days of readministration. It is highly improbable that three-quarters of the reactions would appear within a 2-day period unless there were a preëxisting allergic state. Therefore, we believe that an interval between courses plays a distinct rôle in the demonstration of sensitivity.

The data which have been presented lend strong support to the thesis advanced by Longcope[2] that these allergic reactions to sulfonamides belong in the same class of diseases as serum sickness. An important and practical consideration seems to be that many more individuals are sensitized to the drugs than would be predicted from examination of data on initial administration.

Summary and Conclusions. Of 472 patients who received one course of sulfathiazole, 110 exhibited some form of reaction to the drug and approximately one-half of these had allergic reactions.

The percentage of patients developing drug fever on any one day of therapy is given. The curve rises to a peak of 9.9% on the 9th day and thereafter drops sharply. Thus, if a patient has had no reaction after 9 days of therapy, his chances of developing one subsequently on the same administration diminish rapidly.

Of 103 patients receiving sulfathiazole twice, with an interval of from 2 to 180 days between courses, 22 patients exhibited sensitivity reactions.

In the patients showing manifestations of sensitivity on the second course, drug fever occurred within the first 2 days of readministration in all of the patients who had fever on the first course. Three-quarters of them had, however, had no reaction on the first course.

Of the patients who reacted to the second administration but not the first, none developed a reaction before 9 days had elapsed from the time the first course was started.

Evidence has been presented which suggests that the appearance of sensitivity reactions on the second course is not related to the total time the drug is administered, or to the absolute duration of the interval between courses.

Sensitivity reactions on readministration may follow an initial course which may be as short as 2 or 3 days.

No influence of dosage on the incidence of sensitivity reactions was demonstrated.

The short time between the beginning of readministration and appearance of drug fever is regarded as evidence that an allergic state was present at the time the second course was started. An interval between courses serves to demonstrate that an initial administration has sensitized an individual to subsequent courses of the drug.

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FAILURE OF PENICILLIN IN RHEUMATOID ARTHRITIS

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Although the etiology of rheumatoid arthritis is unknown, many factors suggest that this may be at least in part an infectious process. Such a relationship is suggested by the rapid sedimentation rate, signs of inflammation in the affected joints, fever, tachycardia, loss of weight, positive agglutination reactions to Lancefield group A hemolytic streptococci in more than half of the cases when the disease has been present for 6 months or longer, and a history of preceding upper respiratory infection in some instances.

At present, therapy for rheumatoid arthritis is far from satisfactory. Although most rheumatologists are agreed upon the use of such measures as physical and mental rest, rest of the affected joints, adequate physical therapy, orthopedic care, a sensible high caloric, high vitamin, anticonstipation diet, psychotherapy and symptomatic care, various pseudoremedies have been tried in the past several decades with, in most instances, very little measure of actual benefit. Such substances as bee venom, sulfur, chaulmoogra oil and similar preparations are no longer employed in most arthritic clinics. Sulfonamides have not proved of value in rheumatoid arthritis. The supposed specific immunizing value of vaccines has also been disproved when it was shown that similar symptomatic improvement followed comparable doses of physiologic saline given subcutaneously or intravenously. The value of massive doses of vitamin D in rheumatoid arthritis is questionable; the majority of the larger arthritis clinics believe that no permanent beneficial effect is produced.

The single chemotherapeutic agent which appears to be of definite value at present in rheumatoid arthritis is parenterally injected gold in the form of gold salts. However, gold salts are not the final answer to the therapy of rheumatoid arthritis inasmuch as they are toxic; some patients with rheumatoid arthritis are not improved following gold therapy, and relapses are not infrequent following cessation of chrysotherapy.

Methods. Six patients with typical rheumatoid arthritis were selected; 5 of these were females. In 5 of these individuals, the rheumatoid arthritis was of at least 4 years duration and 3 of the patients had been followed carefully throughout this period. In 1 instance, the rheumatoid arthritis had begun in childhood (Still's disease) and had later become quiescent—only to flare up 5 years later. In another patient, the typical rheumatoid arthritis was apparent for only 8 weeks prior to treatment.

In all instances, penicillin was injected intramuscularly (into the gluteal or deltoid muscles) every 3 hours, day and night for at least 2 weeks. Total dosage was never less than 100,000 units per 24 hours. In 2 of the patients, 200,000 units was given per 24 hours for 1 week, in addition to a further 2 weeks or more of therapy with 100,000 units per 24 hours. Three patients were treated continuously for 4 weeks each; 2 were treated with penicillin for 3 weeks, and 1 received penicillin for only 2 weeks.

The penicillin was dissolved in physiologic saline so that each 100,000 units were mixed with 16 cc. of physiologic saline: when a dose of 100,000 units per day was employed, 2 cc of this mixture was given every 3 hours day and night. The solution was freshly prepared each day, and was kept in the ice-box between injections.

Sedimentation rates were performed every 4 to 7 days by the Rourke-Ernstene method.

All of the patients were hospitalized; 3 were ward patients and 3 were in private or semi-private rooms. All of the patients showed active rheumatoid arthritis clinically when penicillin therapy was begun and sedimentation rates were repeatedly elevated in all instances before the onset of therapy. The typical findings of rheumatoid arthritis were evident: spindle shaped swellings of multiple, symmetrical proximal interphalangeal joints, involvement of the metacarpophalangeal joints, low grade fever, tachycardia, loss of weight, muscular atrophy in some instances, demineralization of bones, soft tissue swelling and narrowing of the joint space by Roentgen examination, anemia and rapid sedimentation rates.

One patient who had been treated for long periods by massive doses of vitamin D (in another institution) showed multiple areas of calcification in both kidneys. One patient had received gold therapy in another hospital several years prior to this period but was forced to discontinue chrysotherapy because of the development of purpuric manifestations. The other 4 patients had been treated by conservative measures.

During the penicillin therapy, conservative measures such as physical therapy, a sensible diet, splinting of affected joints and the use of mild analgesics when required were continued.

Case Reports. Case 1. O. F., aged 22, colored female, was admitted on 8/25/44. She was first seen in 1937 at the age of 15 at which time her chief complaints were stiffness and swelling of the wrists and knees, and fusiform swelling of the proximal interphalangeal joints of most of the fingers. She had lost 40 pounds in the 2 years prior to that time. Physical examination in 1937 showed marked emaciation, fusiform swelling of the proximal interphalangeal joints, swollen, stiff ankles and elbows, and marked muscular wasting. The patient was treated conservatively and her general condition improved gradually.

In the spring of 1944, there was a recurrence of activity of her arthritis with marked increase in joint pain, swelling and stiffness, fever, rapid sedimentation rate, tachycardia, effusion in both knee joints, considerable limitation of motion in the elbows, hips and knees and advanced deformities of the hands. Roentgen examination revealed typical findings of long-standing rheumatoid arthritis with demineralization of bone and marked narrowing of the joint spaces.

Corrected sedimentation rates (using the simplified Rourke-Ernstene method) prior to the administration of penicillin were: 7/3/44, 64 mm.; 7/6, 49 mm.; 7/10, 55 mm.; 8/24, 60 mm.; 8/31, 50 mm.; 9/1, 48 mm.

Penicillin therapy was begun on 9/2/44; 100,000 units was given daily intramuscularly in divided doses every 3 hours day and night for a period of 28 days. Corrected sedimentation rates following penicillin therapy were: 9/8, 44 mm.; 9/13, 42 mm.; 9/18, 60 mm.; 9/22, 47 mm.; 9/25, 44 mm.; 9/28, 44 mm. (penicillin therapy was stopped on 9/30); 10/10, 57 mm.

The rheumatoid arthritis was not evidently affected either subjectively or objectively during or within 4 weeks following the termination of a total of 2,800,000 units of penicillin. Sedimentation rates remained essentially the same.

Case 2. M. E., white married female, aged 32, was admitted 6/20/44, with findings typical of rheumatoid arthritis. She had been well until the spring of 1938, at which time she developed swelling and stiffness of multiple, symmetrical, proximal interphalangeal and metacarpophalangeal joints, followed by pain, swelling and stiffness in the knees, feet and other joints. Treatment at another institution included (over a period of several years) injections of

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sulfur, vaccine and gold. The latter was stopped because of the development of purpuric spots. The patient was fairly well from June 1942 until May 1944 at which time there was a marked aggravation of her joint pain, swelling and stiffness in multiple joints (hands, elbows, wrists, knees and ankles). The patient was forced to go to bed in June 1944. She had lost 10 pounds in the month prior to the present admission.

Physical examination on this admission revealed tender, swollen knees, wrists, elbows, ankles, feet and proximal interphalangeal joints and metacarpophalangeal joints, with ulnar deviation of the fingers, and marked limitation of motion in the elbows and knees.

Laboratory examination showed a moderate hypochromic anemia, normal renal function, typical Roentgen appearance of rheumatoid arthritis and increased sedimentation rate. Sedimentation rates prior to penicillin therapy were: 6/21, 96 mm.; 7/3, 84 mm.; 7/10, 98 mm.; 7/19, 85 mm.; 7/26, 90 mm.; 7/28, 70 mm.

Penicillin was begun on 7/29/44 in divided doses intramuscularly every 3 hours day and night; 100,000 units was given each 24 hours from 7/29/44 until 8/17/44 at which time the dose was increased to 200,000 units per day; this latter dose was continued for an additional week. The patient received a total of 3,300,000 units of penicillin over a period of 4 weeks. Sedimentation rates following penicillin were as follows: 8/3, 75 mm.; 8/8, 68 mm.; 8/11, 75 mm.; 8/23, 85 mm.; 8/28, 100 mm.

There was no apparent improvement either subjectively or objectively in the arthritic picture during penicillin therapy or within a period 7 weeks following the conclusion of penicillin therapy. The patient thought that she felt somewhat stronger following the penicillin therapy but could notice no change in the pain, swelling or stiffness.

CASE 3. S. E., a white male of 34, was admitted to the University Hospital 4/24/44 with a typical picture of rheumatoid arthritis. The patient was well until 1940 at which time he noticed intermittent swelling of the ankles and knees. This joint swelling, pain and stiffness gradually appeared in the hands, wrists, elbows and other joints. Within the year prior to admission, there was considerable limitation of motion and the symptoms progressed to such a stage that crutches were required for walking. He lost 30 pounds of weight in the past year.

Physical examination revealed typical fusiform swelling of the proximal interphalangeal joints of the fingers, metacarpophalangeal joint swelling, ulnar deviation of the fingers, marked swelling and limitation of motion of the elbows, knees and ankles and evidence of marked loss of weight and muscular atrophy.

Laboratory tests revealed a moderate hypochromic anemia, typical Roentgen findings of rheumatoid arthritis and a rapid sedimentation rate.

Sedimentation rates prior to penicillin therapy were: 5/8/44, 39 mm.; 6/5, 58 mm.; 7/17, 65 mm.; 7/26, 50 mm.; 7/28, 59 mm.

Penicillin was begun on 7/29/44 and a total of 100,000 units was given intramuscularly each day from 7/29/44 until 8/12 (a total of 1,400,000 units of penicillin). Sedimentation rates following the injection of penicillin were: 7/31/44, 53 mm.; 8/3, 54 mm.; 8/10, 55 mm.; 8/18, 60 mm.

No subjective or objective improvement was seen during the course of penicillin therapy, or for a period of 2 months following this therapy.

CASE 4. B. M., a married white female of 35 years, developed pain, swelling and stiffness in the right wrist 7 years ago. Since that time, there has been progressive involvement of the feet, knees, elbows, hands and other joints. In the past year, she lost 12 pounds in weight. Physical examination revealed fusiform swelling and tenderness of the wrists, elbows, knees and ankles. There was a moderate hypochromic anemia. Roentgen ray examinations revealed changes typical of rheumatoid arthritis in multiple joints with demineralization of bones, narrowing of joint spaces and fusiform soft tissue swelling.

Sedimentation rates prior to penicillin therapy were: 7/18/44, 38 mm.; 7/21, 35 mm.; 7/26, 40 mm.; 7/30, 33 mm.

Penicillin was begun on 7/31/44 and was continued in a total daily dosage of 100,000 units until 8/29/44—a total of 2,900,000 units being given. Sedimentation rates following penicillin therapy were: 8/2, 36 mm.; 8/4, 42 mm.; 8/8, 40 mm.; 8/14, 37 mm.; 8/17, 35 mm.; 8/21, 45 mm.; 8/28, 38 mm.; 9/5, 42 mm. There was no apparent improvement either subjectively or objectively during the course of penicillin therapy.

In contrast to the failure with penicillin, it might be worth while recording the results of gold administration in this patient. Gold therapy (calcium aurothiomalate) was begun on 9/8/44 (10 days after the last injection of penicillin). After the 4th week of chrysotherapy, the patient began to notice much less pain and swelling in the affected joints (particularly the hands, knees and ankles) and the swelling in these joints was visibly decreased. The sedimentation rate began to fall at this time and had returned to normal after 6 weeks of gold therapy. Not over 25 mg. of calcium aurothiomalate was used at any one dose. Injections of gold salts were given intramuscularly each week after the first 2 weeks (during which early period 2 small injections —10 mg. each—were given each week). The details and results of chrysotherapy in rheumatoid arthritis will form the basis of a separate report.

The sedimentation rates following institution of gold therapy were: 9/12/44, 48 mm.; 9/19, 43 mm.; 9/25, 40 mm.; 10/2, 28 mm.; 10/9, 22 mm.: 10/16 12 mm.: 10/23, 10 mm.; 3/10/45, 8 mm.

This patient has improved steadily both subjectively and objectively since the 4th week of gold therapy.

CASE 5. This 47 year old white married woman (S. H.) was admitted 7/27/44 with a typical rheumatoid arthritis of 12 years duration. She had previously received various forms of treatment, including several courses of "Ertron" capsules (containing 50,000 units of vitamin D) varying from 3 to 6 per day for some months at another institution. Despite therapy, she had progressed intermittently so that on admission, there was a moderate amount of crippling deformity of the fingers with ulnar deviation of the hands; swelling, tenderness and flexion contracture of the knees; marked limitation of motion and tenderness of the elbows, shoulders, feet and other joints. Urogram revealed multiple, small urinary calculi bilaterally similar to the calcium deposits seen in hyperparathyroidism. It is distinctly possible that these may have resulted from the massive doses of vitamin D which she had taken.

Roentgen examination revealed marked demineralization of bones, marked narrowing of the joint spaces, cystic areas near the ends of the bones, soft tissue fusiform swelling of the proximal interphalangeal joints and the evident deformities. A moderate hypochromic anemia was present. Sedimentation rates prior to penicillin therapy were: 7/27, 96 mm.; 7/29, 104 mm.; 8/1, 94 mm.

Penicillin was then begun intramuscularly on 8/2/44 and was continued in a total daily dosage of 100,000 units until 8/16/44, at which time the dose was increased to 200,000 units per day for an additional 8 days—a total dosage of 3,000,000 units of penicillin. Sedimentation rates following penicillin therapy were: 8/8/44, 110 mm.; 8/16, 130 mm.; 8/21, 100 mm.; 8/24, 114 mm.

The patient left the hospital at this time. A sedimentation rate 5 weeks later, 10/6/44, was 115 mm. There was no evident subjective or objective improvement in the arthritic picture.

CASE 6.—M. A., a 35 year old married woman, developed slight pain and swelling of the proximal interphalangeal joints of the second, third and fourth fingers of the left hand about the end of June 1944. There were also mild aches and pains in the ankles and knees. The patient had lost 10 pounds of weight in the following month and showed on laboratory examination a moderate hypochromic anemia and a slightly increased sedimentation rate. Roentgenograms of the hands showed only slight bony demineralization and fusiform soft tissue swelling of the proximal interphalangeal joints. There was no evidence of gonorrhea; gonococcus complement fixation test was negative. There was no history of rheumatic fever. Sedimentation rates were as follows: 8/15, 28 mm.; 8/22, 25 mm.; 8/29, 35 mm.

Although some early cases of rheumatoid arthritis may respond to con-

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servative care with rest of the patient and of the involved joints, physical therapy, adequate caloric and vitamin intake and symptomatic care, such improvement is not usually rapid. It was, therefore, thought that this patient represented a suitable early case of rheumatoid arthritis for trial of penicillin therapy. Penicillin was begun on 8/30/44 and was continued in a daily total dose of 100,000 units per day for 3 weeks (a total dose of 2,100,000 units). During this period, the joint pain and swelling gradually increased and new joints became involved. The stiffness, pain and swelling of the fingers increased definitely during such therapy. Sedimentation rates during and after penicillin therapy were: 9/5/44, 32 mm.; 9/12, 38 mm.; 9/19, 44 mm.; 9/26, 46 mm.; 10/10, 40 mm.; 10/19, 43 mm.

The arthritis definitely progressed and became worse during penicillin therapy.

Comment. Six patients with typical rheumatoid arthritis were treated for from 2 to 4 weeks with penicillin during the acute or subacute stage of their disease. The total dose of penicillin varied from 1,400,000 to 3,300,000 units. Five of the 6 patients received more than 2,000,000 units. In all cases, the penicillin was administered intramuscularly in divided doses every 3 hours day and night.

All of the patients showed joint swelling and pain and an increased sedimentation rate before penicillin therapy. There was no evidence that penicillin altered the course of the disease in any of the patients. In 5 of these patients the arthritis had been present for periods of 4 years or more; all of these showed activity of their rheumatoid arthritis at the time of penicillin administration. The sixth patient presented an early rheumatoid arthritis of only 8 weeks duration prior to penicillin therapy. In Case 1, the arthritis had been inactive for several years but the active process recurred 5 months prior to penicillin administration.

Summary. There was no subjective or objective evidence of improvement in 6 patients with active rheumatoid arthritis following the administration of penicillin intramuscularly in total doses varying from 1,400,000 to 3,300,000 units given over periods varying from 2 to 4 weeks.

FOCAL ELECTROENCEPHALOGRAPHIC CHANGES DURING THE SCOTOMAS OF MIGRAINE

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In a recent communication[1] we have described a migraine-like syndrome complicating decompression sickness. This was characterized by scintillating scotomas, homonymous visual field defects, rarely other focal neurologic signs, and headache, the latter usually contralateral to the scotomas. These symptoms always occurred after

decompression sickness had developed but they were unrelated to altitude. Most often they developed 5 to 30 minutes after descent, but when they did develop at altitude their course was the same whether the subject remained at altitude or was brought down. The

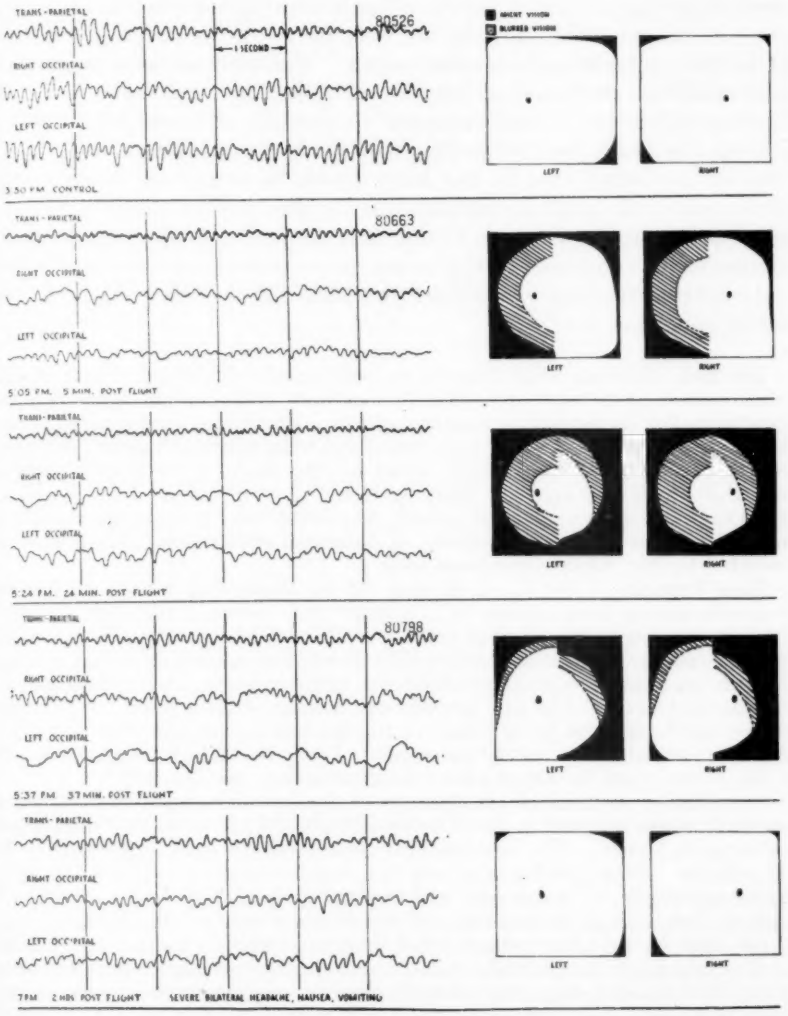

FIG. 1.—Electroencephalogram and visual fields during the scotoma-migraine syndrome complicating decompression sickness. Note the appearance of irregular 4 to 7 per second waves from the occipital region contralateral to the visual field defect. The transparietal tracing remained unchanged. The electroencephalogram was normal during the period of severe headache.

reaction tended to occur repeatedly in certain individuals and not at all in others. A statistical analysis of the past incidence of headaches having the character of migraine regardless of frequency or intensity revealed a highly significant positive correlation among the scotoma

susceptible subjects. It is our opinion that this reaction is mediated through a vascular mechanism which is similar to, if not identical with, that described in clinical migraine by Wolff and his associates.[3]

Electroencephalographic studies in 2 instances of this syndrome revealed focal changes in the cortical areas corresponding to the neurologic signs and symptoms. The homonymous visual field defects were accompanied by slowing and irregularity of the potentials arising from the contralateral occipital cortex. The electroencephalographic abnormalities continued as long as the neurologic signs persisted, following which the record returned to normal and remained normal during the headache. (See Fig. 1.) Gibbs,[2] in a discussion of these studies, remarked that he had been unable to obtain any comparable electroencephalographic findings during the visual disturbances of clinical migraine. Because of the close similarity in all other respects between this syndrome complicating decompression sickness and clinical migraine, it seemed important to obtain similar observations in the latter condition.

Method. Electroencephalograms were obtained on 3 subjects with migraine while experiencing scotomas. In all instances abnormalities were demonstrated in the corresponding occipital cortex. Electrodes were applied at the lateral tips of the inion which were considered to be reasonable approximations of the projection of each visual cortex on the skull. In 1 case 2 parietal electrodes were also applied. Because of the short duration of the scotomas the electrodes were applied as quickly as possible and records taken until a normal pattern had been regained. A 3-channel electroencephalograph, constructed by Mr. Albert Grass, was used.

Case Reports. CASE 1. A 38 year old physician with history of typical migraine dating back to age 14. Mother and maternal aunt both suffered from severe migraine. Typical attacks are heralded by drowsiness on arising in the morning. This is then followed by slowly increasing hemicrania, accompanied by nausea, salivation, chilliness, breathlessness, and evacuation of bladder and bowel. The pain is bright and bounds with the pulse. The hemicrania can be relieved by occlusion of the ascending temporal branches of the external carotid artery on the same side. The entire attack usually occupies ½ day. For years the attacks have occurred about once a month.

Scintillating scotomas as prodromata of the headache were first observed about 13 years ago, and in all 30 to 40 such attacks have occurred during the subsequent 5 years. The scotoma was usually on the right and lasted 10 to 20 minutes. Other prodromata have been numbness and tingling of the right upper extremity, 11 years ago, and expressive aphasia (9 years ago); each episode lasted about 30 minutes and was followed by excruciating headache.

On June 30, 1944, the patient noted onset of scintillation and loss of vision in the right upper visual field. Gross confrontation revealed a homonymous visual field defect in this area. Scintillation was apparent with the eyes either open or closed. Electrodes were applied as quickly as possible at the lateral borders of the inion; monopolar tracings were obtained from the right occipital and the left occipital regions and a bipolar tracing from the transoccipital. These are illustrated in Figure 2. The scintillation, which lasted a total of 15 minutes, was present, but receding peripherally, during the first 3 minutes of recording. The tracing from the left occipital region revealed irregular low voltage slow activity which was not present on the right side. As the scotoma disappeared to the periphery the left occipital tracing revealed slower and higher voltage activity for 1 minute and then progressively improved; 6 minutes after scintillation had vanished the tracings from both occipital regions were normal and synchronous. Left-sided headache began shortly thereafter.

Comment on Case 1. Focal electrical abnormalities arising from the occipital cortex corresponding to the homonymous visual field defect are clearly demonstrated in this case. The fact that the electroencephalogram became more abnormal during the first minute after the scotoma had disappeared is probably explained by inaccurate electrode placement. Were the electrodes placed over a relatively silent area of occipital cortex, increase in abnormality as the disturbance receded from the visual field seems entirely plausible. It will be noted that this phenomenon lasted only 1 minute after subjective appreciation of scintillation had disappeared and that complete return of the electroencephalogram to normal required only 5 minutes.

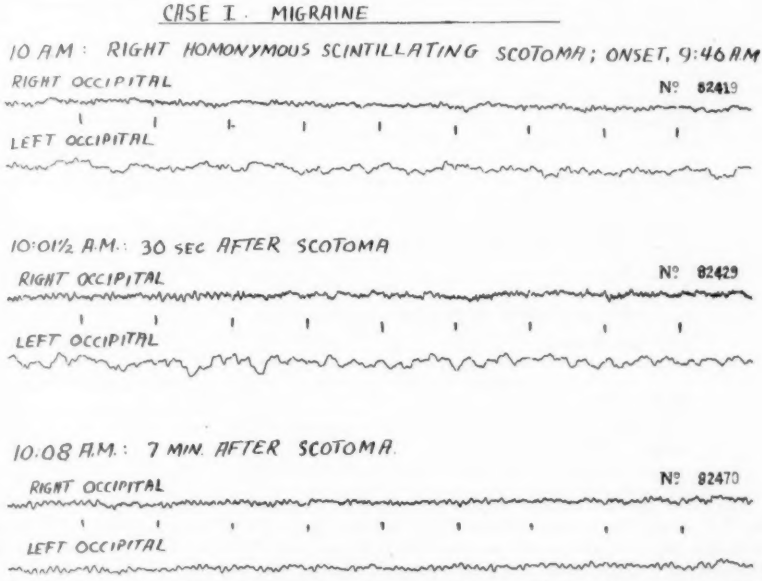

FIG. 2.—Case 1. Note the low voltage slow waves from the left occipital region during right homonymous scintillating scotoma. For the first minute after the scotoma disappeared the voltage of the slow waves became higher. Seven minutes later the record was completely normal. Headache had not yet begun.

CASE 2. A 39 year old physician had experienced occasional mild headaches in childhood. Seven years ago he first experienced severe hemicrania associated with nausea and vomiting, lasting 5 to 6 hours. A second severe attack occurred 6 months later. Many very mild unilateral headaches have occurred since then. Two years ago the development of decompression sickness during exposure to high altitude in a decompression chamber was followed on 5 occasions by scintillating scotomas, homonymous visual field defects, and subsequent mild contralateral headache. Since then the patient has had 4 episodes of spontaneous scotoma, 1 on the left, 3 on the right. All occurred in the morning and were followed by mild contralateral headache lasting the remainder of the day.

At 9:30 A.M., June 8, 1944, onset of scintillating scotoma in the upper quadrant of the visual field was noted. Brief confrontation revealed a right homonymous upper quadrantic defect. Electrodes were applied as in Case 1. After some tracing had been obtained, parietal electrodes were also applied. The results are illustrated in Figure 3. Tracings were obtained during the

last 5 minutes of the scotoma, as it receded peripherally. Irregular, low voltage slow waves, frequency, 4 to 7 per second, with some admixture of alpha activity, were obtained from the left occipital region. Regular, 9 to 10 per second alpha activity was obtained from the right occipital region. As the scotoma disappeared, a few bursts of slow waves were still to be seen from the left occipital, while the activity from the right occipital and transparietal regions remained normal. With the appearance of left-sided headache the electroencephalogram returned to normal.

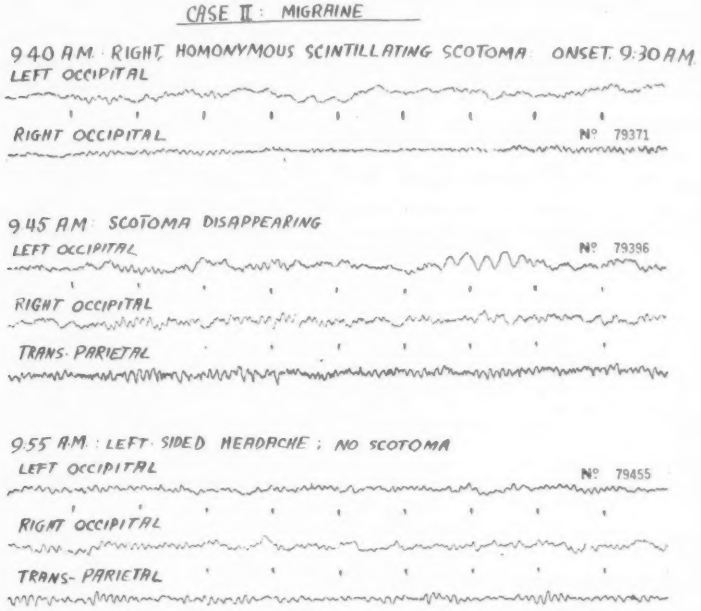

FIG. 3.—Case 2. Absent alpha activity and irregular low voltage slow waves from the left occipital cortex during right homonymous scintillating scotoma. Tracings from the left occipital and transparietal regions were normal. Ten minutes after the scotoma had disappeared the electroencephalogram was normal. Left-sided headache had begun.

CASE 3. A 26 year old resident physician has experienced episodes of scintillating scotoma and headache during the past 7 years. These incidents often have their onset during reading and he is aware of gross visual field defects. The headache is sharp, moderately severe, radiates from frontal to occipital region, and is contralateral to the scotoma. The scotomas are sometimes bilateral. The headache is usually alleviated by 10 to 20 gm. of aspirin or ½ gr. codeine within 1 hour. Gastro-intestinal symptoms have not been present. These episodes have occurred as frequently as 8 to 15 times a year often during periods of emotional tension.

At 3:15 P.M., June 17, 1944, a scintillating scotoma appeared in the right homonymous visual field. This gradually moved to the periphery, but at the end of 1 hour was still present. At 4:30 P.M. electrodes were applied and electroencephalographic tracings were obtained. At this point the subject was aware of scintillation in the extreme periphery of the right homonymous visual field which came and went at 20 to 30 second intervals, lasting 10 to 15 seconds at a time. At less frequent intervals slight scintillation was noted in the left field as well. The subject was asked to indicate the appearance and disappearance of the scotoma. The findings are illustrated in Figure 4. With the appearance of scintillation on the right, the tracing from the left occipital

region revealed loss of alpha activity and low voltage slow waves. Alpha activity returned when the scintillation disappeared. Similar, but less striking alterations were recorded from the right occipital region during the fluctuating left-sided scintillation. Twenty minutes of tracing were obtained. The fluctuating scintillation lasted another 20 minutes and was followed by bilateral headache. An electroencephalogram obtained 2 days later when no symptoms were present revealed sustained and symmetrical alpha activity from both occipital regions.

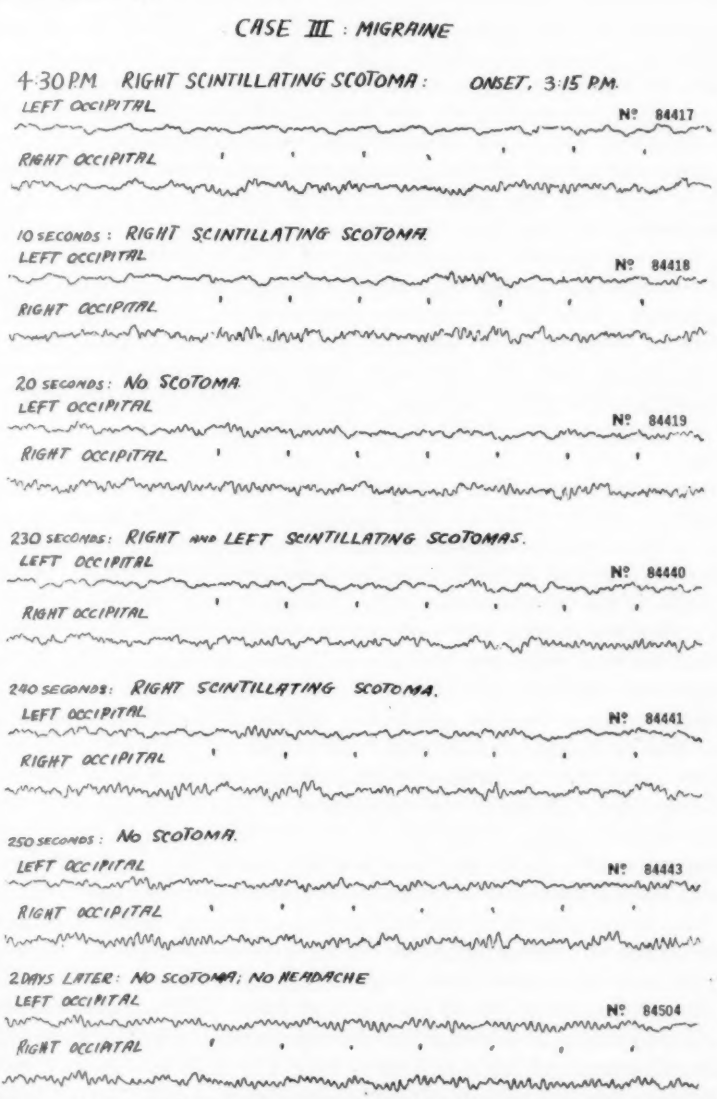

FIG. 4. Case 3. After 75 minutes right and left scintillating scotomas were in the extreme periphery of the visual fields and were waxing and waning in intensity. With each reappearance of the scintillation there was loss of alpha activity and low voltage slow activity from the corresponding occipital cortex. This was observed more consistently from the left occipital cortex than from the right. Two days later sustained alpha activity was found arising from both occipital regions and there were no symptoms.

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Discussion. Although only 3 cases are presented, the results are so clear-cut as to allow little question as to their validity. Indeed, considering the difficulties of timing and of electrode placement the ease with which the focal abnormalities were demonstrated was unexpected.

Schumacker and Wolff[3] have presented convincing evidence that the focal neurologic signs of migraine, of which scintillating scotoma are the most common, are the result of spasm of intracerebral vessels, while the headache results from dilation of the pain-sensitive extracranial branches of the carotid artery. More specifically, the scotoma are thought to result from spasm of branches of the posterior cerebral artery, with ischemia of portions of the occipital cortex. The homonymous nature of the visual field defects, the sparing of central vision, the peripheral spread of the scotoma, and the efficacy of vasodilator drugs in relieving the scotoma all favor such a mechanism. The demonstration of irregular, slow waves in the electroencephalogram from the occipital cortex corresponding to the visual defect offers additional evidence for the existence of such areas of local cortical ischemia. The prompt return of the electroencephalogram to normal following scotoma of brief duration and the remarkable simultaneous waxing and waning of both the scotoma and the electroencephalographic abnormalities following a scotoma of longer duration, as illustrated in Case 3, are quite consistent with the behavior of vasospastic phenomena.

The syndrome complicating decompression sickness resembles clinical migraine so closely that we have postulated an identical mechanism and have ventured the suggestion that it may possibly be true migraine provoked in susceptible individuals by decompression sickness. Indeed, the failure of previous investigators to demonstrate electroencephalographic changes during the scotoma of clinical migraine represented the chief point of difference between the two syndromes. The data of this paper obviate this difficulty. The only significant difference now remaining between the two syndromes relates to the relative intensity of the focal neurologic (vasospastic) signs and of the headache (vasodilation). In the syndrome complicating decompression sickness the vasospastic phenomena are prominent while the headache is often mild; in clinical migraine the reverse is more often true.

Summary. Abnormal electrical activity from one occipital cortex has been demonstrated in 3 instances of spontaneous scintillating scotoma with homonymous visual field defect occurring during attacks of clinical migraine. Irregular, slow waves were recorded from the contralateral occipital cortex while regular normal activity was recorded from the ipsolateral occipital cortex, and from both parietal regions. With disappearance of scotoma the electroencephalographic abnormalities also disappeared, although in 1 case the pattern became more abnormal for the first minute after the scotoma had disappeared before returning to normal. It was thought this might relate to inaccurate electrode placement. The record was normal during the beginning of the headache.

These data confirm the results previously obtained during examples

of a migraine-like syndrome occurring as a complication of decompression sickness and further emphasize the analogy between that syndrome and clinical migraine. One of the subjects in this report had also experienced scotomas and headache after decompression sickness. The results also are consistent with the vasospastic nature and cortical origin of the scintillating scotoma of migraine as postulated by H. S. Wolff and his associates.

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INITIAL CARDIAC EXAMINATION OF 23,000 INDUCTEES AND VOLUNTEERS

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Many cardiac problems of wartime have been presented to date. In general, White[22a] discussed the Army, and Duncan[6] the Navy viewpoints. From the individual service examiners have come the reports by Ungerleider, Duhigg and Gubner,[20] Master,[13] and Wilburne and Ceccolini.[23a] Statistical studies of selective service records were those of Rowntree.[15]

More important, from the cardiac standpoint, was the report of the reëxamination of 4994 men disqualified for general military service because of the diagnosis of cardiovascular defects.[11a] This combined study,[8a] made by special medical advisory boards in Boston,[22b] Chicago,[8b] New York,[11c] Philadelphia,[19] and San Francisco,[10] was subsequently published in detail. The findings of an initial cardiac examiner have not been presented.

From February 5, 1943, to June 21, 1944, I, among many others, had the unusual privilege of serving as a civilian physician on part-time, temporary duty, attached to a chest section of a medical unit at the Armed Forces Induction Station in Chicago. Civilian doctors constituted the backbone of the examining groups at these stations.[15c] During this period I examined 23,000 men between the ages of 17 and 38 years who were sent to the Induction Station by the Selective Service Boards in the State of Illinois. The men included those who

* The opinions and assertions expressed herein are those of the writer, and are not to be construed as those of any member or branch of the Armed Forces.

were going into the Army, Navy, Marine Corps, and Coast Guard, if accepted for service.[18] This study does not include men of 38 years and over who volunteered for special units, such as the Seabees and Ship Repair. The 23,000 men were fairly representative of the normal male adult population in that age group.

Although the chest section was responsible for all heart and lung conditions, asthma, and hay fever, questions concerning which were asked of all examinees, this report is based only on the cardiac examination. A routine procedure was followed which precluded the omission of any part of the cardiac examination. All men were asked the same questions as to previous known heart trouble, the cardiac area was auscultated at various points, and the blood pressure was estimated. Even before this was done, the cardiac examination really began as the man stepped into view. Unusual apprehension, malar flushing, cyanosis of the lips, and abnormal pulsations in the neck, arms, or chest were noted. Such signs were rare among this large group, but the notation of any of these findings attracted much closer attention to the subject.

The task of the civilian examiner was to weed out those with a history and/or findings of heart disease according to the mobilization regulations. This job was of much greater significance than it seemed to be at first. During the period stated I examined on the average of 20 men per hour; the average number of hours worked per day was 4.7. The constant problem of error, in that one might do an injustice to both the Armed Forces and the examinee by overlooking any cardiac disturbances in such a steady flow of men, had to be kept in mind at all times.

Heart disease is often perfectly compatible with normal activity, even for the strenuous physical demands occasioned by service in the Armed Forces. However, because of the eventual limitations which tend to develop in most types of heart disease, it was not deemed advisable to accept men with definite heart disease for service, since permanent obligations are assumed by the government for its military personnel.[20] All men were subjected to a chest photo-roentgenogram, but only those weeded out for cardiac reasons received further diagnostic work-up along these lines, which was at the discretion of the medical officers in the chest section.

Among the 23,000 men which I examined there were 1621 (7.4%) who gave a history or had the physical findings of heart disease (Table 1). These 1621 men were referred to the medical officers in the chest section, with the reason for doing so slipped on the bucksheet[5] that went along with each man. The leading cardiac causes for referral were (1) a history of heart trouble, physical findings absent, (2) tachycardia, (3) an elevation of blood pressure above 148/88, and (4) murmurs.

Only 226 (1%) had organic heart disease, however. This compares favorably with a study of 20,000 examinees in the Pacific Northwest by Wilburne and Ceccolini.[23b] They noted heart disease in 288 (1.44%), but their Selective Services examinees were 20 to 45 years of age, which accounts for the higher incidence. It is difficult to com-

pare my figures with others previously reported because mine are not based on the percentage of the total number of men rejected.

TABLE 1.—CARDIAC HISTORY AND FINDINGS AMONG 23,000 INDUCTEES AND VOLUNTEERS

	Number	Percentage
1. History, physical findings absent	659	2.8
2. Tachycardia	351	1.5
3. Hypertension	327	1.4
4. Rheumatic heart disease	203	0.9
5. Congenital heart disease	20	0.1
6. Thyrotoxicosis	32	0.15
7. Ventricular extrasystoles	15	0.08
8. Luetic aortic insufficiency	3	
9. Auricular fibrillation	3	
10. Bradycardia (digitalis)	2	
11. Bilateral splanchnicectomy (juvenile hypertension)	1	
12. Lutembacher's syndrome	1	
13. Postoperative myxedema	1	
14. Hypothyroidism	1	
15. Situs inversus	1	
16. Pernicious anemia	1	
Total referred	1621	7.4
Total organic heart disease	226	1.0

TABLE 2.—PERCENTAGE OF REFERRALS IN EACH OF THE GROUPS

	Number	Percentage
1. History, physical findings absent	659	40.7
2. Tachycardia	351	21.8
3. Hypertension	327	20.3
4. Rheumatic	203	12.4
5. Congenital	21	1.3
6. Thyrotoxic	32	1.9
7. Luetic	3	0.1
8. Arrhythmias	3	0.1
9. Miscellaneous	23	1.4
Total	1621	100.0

History of Heart Trouble, Physical Findings Absent. This was the largest and most difficult group with which the chest examiner had to contend. It has not been mentioned previously. Of the 23,000 examinees, 659 (2.8%) gave a history of heart trouble, but there were no cardiac findings. The most common story given by the examinee was that he had a "leakage of a valve" or a "murmuring of the heart," which had been found on a previous examination from 1 day to 37½ years earlier. The same held true for the complaints of an "athlete's" or enlarged heart, a rapid pulse, and high blood pressure. Sometimes the examinee used such terms as "tachycarditis," or "macrocarditis," or that he was treated for "blood pressure." Careful questioning along these lines usually brought out that he had been examined very infrequently, if at all, since the original findings. Some examinees made self-diagnoses because of symptoms generally attributed to heart disease or popularly thought to be due to hypertension. Any man with a history of acute rheumatic fever or of rheumatic heart disease, either during childhood or of more recent origin, which had confined him to bed for weeks or months, despite a lack of abnormal physical findings, was investigated further. It would have been

much easier to overlook many of these men who had cardiac complaints without findings, but the medical officers in the chest section requested that these men be referred to them for further examination. Such an inductee, who was reëxamined carefully, had his morale boosted immeasurably by the thoughtfulness of the medical officer. Fully a third of the 1621 examinees who I weeded out of the line accepted the decision of the medical officers graciously. From the standpoint of the ultimate disposal of the inductee, the time taken for this group of men was of untold value. A man who complains constantly about his "heart trouble" is of no use, military or otherwise. If this percentage in the group under consideration was consistent for the nation,[15c] a total of 364,000 men gave a history of heart trouble but physical findings were absent. Probably the major accomplishment of the medical officers at the Armed Forces Induction Stations can be attributed to the wisdom of those in the chest sections in their handling of such a large group of complainants.

Tachycardia. The second important problem was the range of the pulse. MR 1-9 state that a truly persistent heart rate of 100 or over should be considered a cause for rejection. As emotion raised the pulse very easily, it had to be ruled out as a factor. All the more so at this station where the chest examination followed the interview with the neuropsychiatrist. Moreover, the heart rate is considered one of the poorest criteria of cardiovascular fitness.[11a] There were 351 men (1.5% of the 23,000 examinees and 21.8% of those referred) who had a tachycardia. The combination of a rapid cardiac rate and an elevated blood pressure on the initial examination in the sitting position was common. Tactful handling of the inductee was an important factor. Generally, if the rapid rate persisted, it was above 120 and other signs of neurocirculatory instability were present. No satisfactory relationship between the basal pulse rate, sitting pulse rate, and physical fitness for strenuous exertion in normal healthy young men has been noted.[3] Emotional factors were largely responsible for the high resting pulse rates commonly found during the pre-induction medical examination of such men. Brown[4b] stated that during the course of a 12 month period there were only 36 soldiers discharged from the Army at the Station Hospital, Fort Devens, Massachusetts because of organic heart disease. In the same period, however, there were 300 soldiers with the neurocirculatory syndrome at that hospital, nearly 10 times as many as those with organic heart disease. He felt that the presence of a large number of soldiers with neurocirculatory asthenia was a challenge to the examining physicians at the Induction Stations.

Hypertension. The third largest group were those with an elevated blood pressure. In a previous study[9a] I reported that hypertension was the most common cause of organic heart disease regardless of race or sex. MR 1-9, although setting a limit, allows freedom of interpretation and judgment above that limit.[18] A cause for rejection was a "persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, unless in the opinion of the medical examiner the increased blood pressure was due to psychic reaction and not secondary to renal

or systemic disease." There were 327 (1.4%) of the examinees who presented what is probably our most difficult cardiovascular problem. Wilburne and Ceccolini[23a] observed hypertension in 241 (0.96%) of 25,000 Army examinees, and suggested that the incidence is overestimated. The earliest report[1] on the incidence of hypertension among Selective Service registrants was 3.02%.

Opinions differ greatly as to the upper range of blood pressure readings, especially in younger men. White[22a] stated that under the excitement of the examination 160 might be acceptable as the upper limit of the systolic pressure, but he would not raise the diastolic level much above 90 if any. It is evident also that the blood pressure of hypertensives may be notoriously labile.[6,7] In the earliest work on hypertension, Janeway[9b] said he regarded with suspicion any pressure above 135 mm.; and 150 in a young person, when found on several examinations and with due precautions. Lewis[12] felt that values above 160 mm. Hg definitely surpass normal limits, while a diastolic pressure of 100 mm. is generally regarded as definitely abnormal. Russek's observations[16] indicate that a normal person may show little fluctuation in blood pressure in youth, and considerable variability in middle age. Rogers and Palmer[14] directed attention to transient elevations in blood pressure that are observed in men during physical examination for the Armed Forces. During 1 month at the Office of Naval Officer Procurement in Boston, they found 222 (14%) of 1574 applicants had mild variable hypertension at the initial examination; the systolic pressure varied from 140 to 160 mm., and occasionally higher, and the diastolic pressure ranged from 95 to 110 and rarely as high as 120. In Chicago[8b] the special board found that the hypertensives offered the greatest problem. Although this board adhered to the instructions in MR 1-9, it felt that it was here, if any place, that more liberality might have been shown. The New York[11c] reëxamining board stated that the critical levels of systolic and diastolic blood pressure have not been established on a firm basis. However, they added that until further data are available or the need for manpower becomes acute, it would seem wise to adhere to the criteria at present in use, both because of possible future damage to the individual and because of danger of swelling the pension lists for disability.

On the initial cardiac examination in the sitting position many high readings were obtained, not only systolic but also diastolic, due mainly to emotional factors. I found that a few seconds of friendly chit-chat with the examinee, not only to put him at ease but also to bring back his feeling of individuality, and the taking of the blood pressure last, although the cuff was applied before auscultating the cardiac area, avoided many of the temporary high readings. After the psychic factor was handled, and the reading remained above 160 systolic and 100 diastolic on two or more consecutive estimations, then I considered the man a hypertensive. The majority of these men were neither aware of the elevated blood pressure nor did they have any of the psychoneurotic manifestations generally associated with known essential hypertension. This finding not only appears much earlier in life

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than has been assumed, but it has a longer duration than it is generally thought to have.[9c,d,e,f] It must be emphasized that no applicant was rejected as the result of one or two blood pressure readings. When the estimation of the blood pressure was regarded as abnormal, or in case of doubt, the procedure was repeated twice daily (in the morning and in the afternoon) for a sufficient number of days (usually 3), which enabled the medical officers to arrive at a definite conclusion.

TABLE 3.—PERCENTAGE OF VALVULAR LESIONS IN RHEUMATIC HEART DISEASE

	Number	Percentage
Mitral	152	74.8
Aortic	15	7.4
Mitral and aortic	36	17.8
Total	203	100.0

Rheumatic Heart Disease. Although not strictly comparable because the men were 20 to 45 years of age, Wilburne and Ceccolini[23b] reported rheumatic heart disease in 183 (0.9%) of the 20,000 examinees in the Pacific Northwest. In their cases the mitral valve was involved alone in 152 (83.1%), the aortic valve only in 8 (4.4%), and combined mitral and aortic defects were observed in 23 (12.5%). I found 203 (0.9%) of the 23,000 examinees had organic heart disease on this basis. Disease of the mitral valve alone was noted in 154 (74.8%), aortic alone in 15 (7.4%), and combined aortic and mitral lesions were noted in 36 (17.8%).

The murmurs were the essential part of the picture. Only 48% of the 203 examinees gave a history of acute rheumatic fever and/or rheumatic heart disease. Among the remainder the valvular disease was diagnosed for the first time. The timing of the murmur was not as important as its character. A well-circumscribed, forceful apex beat, possibly with a palpable thrill, was suggestive of mitral stenosis, but not pathognomonic, even if noted outside of the left mid-clavicular line. The presence of these findings without a murmur was of no significance. Accentuated pulmonic sounds alone were entirely too common to be given much consideration. The variability of murmurs in mitral stenosis was first noted by Hope.[9g,h,i] In a study of 237 cases of this valvular lesion, I found that the murmurs were readily recognized by the characteristic rasping sound without resorting to definitely isolating the bruits in the cardiac cycle by timing.[9j] This must be borne in mind, for in a series of 835 recruits, Bramwell[2] noted signs simulating mitral stenosis, a duplicated second sound (generally associated with an apical systolic murmur) in 157, all of them acceptable for general service. Furthermore, it has been shown that there is no relationship between the character of rheumatic fever, the number of recurrences, and the age of the patient at the onset, on one hand, and the development of cardiac damage, on the other hand.[4a]

These difficulties were readily appreciated not only by the individual examiner, but also by the reëxamining boards which were able to check the selected examinees carefully. The Boston board[22b] considered this one of their most difficult problems, as did the New York[11c] and the San Francisco[10] boards. The Philadelphia[19] board stated

that of the 160 men rejected for mitral insufficiency without cardiac enlargement, a great many did not have organic heart disease, but the loudness of the murmur in certain positions and following exercise caused rejection, because of the possibility that, if reclassified, they would be discharged from the service sooner or later. The Chicago[8b] board, however, reported that rheumatic heart disease offered no great difficulty except as far as the accuracy in the diagnosis of the lesion was concerned.

Other Conditions. Congenital heart disease was present in only 21 (0.1%) of the 23,000 examinees. This incidence may be compared with that of a previous study made at the Cook County Hospital[21] and that of Wilburne and Ceccolini,[23b] where it was the same.

Comment. There were a variety of other conditions, but only two require comment. Two men, who had bradycardia on the basis of digitalis, took the drug on their own volition as they had heard it was a good "heart tonic." No instance of malingering on this basis was found. The other point of interest was the finding of only 3 (Negro) men with syphilitic aortic insufficiency, despite the known incidence of syphilis among the examinees, 7% of whom were Negroes. This extremely low incidence of syphilitic heart disease, which averaged 13% among cardiacs at the Cook County Hospital[9a] in 1932 and 1933 when 30% of the patients were Negroes, can only be explained by the excellent treatment that most luetics receive, based on the modern public health program. Once aortic insufficiency appears in the young male syphilitic, the interval between the changes in the valve and the appearance of severe cardiac symptoms seems to be comparatively short.[9k] However, the Chicago[8b] reëxamining board, the only one to comment on this, doubted that the true incidence of syphilitic heart disease among examinees is represented by even 0.5%.

It must be emphasized again that this is only the report of one among many civilian physicians who had the good fortune to be able to examine (23,000) inductees and volunteers. The figures given in this study are *not* the number or percentage of those rejected by the Armed Forces. We did accomplish our task, for the elimination of heart ailments was satisfactorily performed in enlistment, recruiting, induction, and training areas.[17]

Summary. While serving as a civilian physician on part-time temporary duty attached to a chest section of a medical unit at the Armed Forces Induction Station in Chicago, I examined 23,000 inductees and volunteers between the ages of 17 and 38 years. Although these were routine initial cardiac examinations, with an average of 3 minutes to each examinee, the results, when compared with other reports of a somewhat similar nature, seem fairly accurate. There were 1621 men (7.4%) who had a history and/or physical findings of heart disease, but only 226 (1%) had organic heart disease.

The largest group was those with a history of heart trouble, physical findings absent, 659 (2.8%). The second largest number was those with tachycardia, 351 (1.5%); third, hypertension in 327 (1.4%), and the fourth, those with rheumatic heart disease, 203 (0.9%).

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Outstanding was the wisdom and tact displayed by the medical officers in the chest section in the handling of all inductees or volunteers who complained of any symptoms relating to or indicative of of heart trouble, for the ultimate benefit of both the Armed Forces and the individual.

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ACUTE SYPHILITIC MENINGITIS

A Discussion of the Problems Encountered in the Diagnosis

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A small proportion of all persons infected with syphilis develop an acute meningitis as the result of an active infection of the meninges by

the *Treponema pallidum*. The diagnosis of this form of syphilis is often difficult. Among 9 cases of acute syphilitic meningitis seen at this hospital during the past 2 years, 5 presented perplexing clinical or laboratory manifestations. It is the purpose of this paper to report these sources of diagnostic error.

Although treponemal invasion of the neuraxis in early syphilis is a frequent occurrence,[6] the production of symptoms of acute meningitis is uncommon. Only 55 of Moore's 2675 cases of early syphilis developed this condition,[9] and reports in the literature usually consist of a relatively small number of cases observed over a period of years.

Acute syphilitic meningitis is most often the result of inadequate treatment, appearing as a relapse phenomenon or neurorecurrence, but occasionally it develops early in the course of luetic infection without previous treatment.

Although pathologically there is a widespread meningeal involvement in all cases of luetic meningitis, the clinical manifestations fall largely into one of three groups. The first consists of basilar meningeal signs, predominantly cranial nerve palsies. The second group is characterized by symptoms referable to the cerebral vertex, such as hemiplegia, aphasia, convulsions or delirium. The third group of patients have all the signs of acute hydrocephalus with headache, nausea, vomiting and choked disks. The occurrence of increased intracranial pressure in this latter group is presumably due to an obstruction of the spinal fluid circulation in the posterior fossa.

The symptoms exhibited by our 9 patients fell into one of these three groups with surprisingly little overlapping or admixture. Each of our patients had early syphilis, usually less than a year's duration. The spinal fluid findings in our cases were similar to those reported in the literature and consisted usually of an increased pressure, pleocytosis, increased protein, and almost always a positive Wassermann test. Since excellent reports on the clinical and laboratory manifestations of this condition have appeared in recent years,[8,9,11,13] only the cases which illustrate certain unusual features will be discussed.

Relation of Syphilitic Meningitis to Previous Treatment. In Merritt and Moore's review on the subject[8] they found only a rare case of acute syphilitic meningitis developing while the patient was taking standard antiluetic treatment. Occasionally the syndrome has been observed to appear during mercury inunction, but its occurrence during bismuth treatment is unusual. In fact, the use of bismuth has been generally thought to protect the patient against neurorelapse.[10] It was for this reason that the diagnosis of acute syphilitic meningitis in 2 of our cases was delayed, both of them having been under bismuth therapy at the time they developed symptoms.

Case Studies. CASE 1. F. J., a 21 year old white girl, was first found to have syphilis in April 1943, when she went to a physician with a generalized skin eruption. The serologic test for syphilis was positive and antiluetic therapy was started with disappearance of the cutaneous lesions. She received 14 weekly injections of neoarsphenamine followed by 8 weekly intramuscular injections of a soluble bismuth preparation. During the course of bismuth therapy she noted the appearance of a headache, which became so severe

that treatment was stopped and the patient remained in bed. Nausea and vomiting, blurred vision, dizziness and tinnitus then developed. All these symptoms became progressively worse and she finally sought hospital admission 8 weeks after their onset.

On admission to the hospital in December 1943, the patient appeared obviously ill, irritable but coherent. There was considerable stiffness of the neck, but the Kernig and Brudzinski signs were negative. The chief neurologic manifestation was a choking of both optic disks. These showed approximately 2 diopters of papilledema with some retinal edema and venous congestion. There were numerous areas of old choroidal pigmentation in both fundi. The other cranial nerves were not affected, the reflexes were normal, and sensory examination was also normal. The heart, lungs and abdomen showed no abnormalities.

The leukocyte count was 5500 per c.mm., and the differential count was normal. The Kahn test of the blood was positive with 200 Kahn units. The spinal fluid contained 286 cells, all lymphocytes, and 285 mg. of protein per 100 cc. The spinal fluid sugar was 59, and the chlorides 640 mg. per 100 cc. The mastic curve was 45554 and the spinal fluid Kahn was positive. Repeated spinal fluid examinations showed essentially the same values with a consistently positive Kahn test.

Course. The oral temperature on admission was 98° F., but fluctuated between 98° and 99.5° F. during the hospital stay. The patient continued to complain of headache until mapharsen therapy was begun on the 6th hospital day. Following the third daily injection of 60 mg. of mapharsen, the patient's temperature became normal and her headache was almost completely relieved.

She received daily injections of mapharsen for 7 days and was then placed on tri-weekly injections of mapharsen for 10 weeks. After 5 weeks the papilledema had disappeared, but no change in the chorioretinitis was observed. After 10 weeks of treatment the spinal fluid contained 4 cells, 38 mg. of protein per 100 cc. and a mastic of 431111. The spinal fluid Kahn was positive and the Wassermann was also positive, using 0.0625 cc. of fluid.

Case 2. J. B., a 28 year old colored female, developed a generalized skin eruption in August 1942, 1 month after marriage. The serologic test for syphilis, which had been negative in June 1942, was found to be positive in October 1942, and antiluetic treatment was begun. Fifteen regular weekly injections of an arsenical compound and 4 injections of an oil suspended bismuth preparation had been given when the patient was forced to stop treatment because of severe headache in January 1943. This was followed during the next few weeks by paresthesias over the right side of the face, deafness of the right ear, tinnitus, nausea and vertigo. She also noted that her mouth drooped on the right side, that she could not close her right eye, and that her smile was "crooked." The headache became progressively worse and she finally was admitted to the hospital in March 1943.

On admission the patient appeared to be a well-nourished Negress, not acutely ill, but complaining of severe headache. The pupils reacted well to light and accommodation and the extraocular movements were normal. The fundi were negative with normal physiologic cupping of the optic disks. There was definite hypesthesia of the right side of the face with weakness of the forehead and facial muscles on the right side. Considerable deafness was present on the right. The tongue protruded in the midline. The neck was not stiff and the lungs were clear. No abnormality was found in the heart and the blood pressure was 140/90. The abdomen was normal, but examination of the rectum revealed a dense stricture 7 cm. above the anus. The deep reflexes were normal, and no sensory disturbances or motor weaknesses of the extremities were noted.

The white blood cells totalled 6100 per c.mm. (neutrophils 61%). The Kahn test of the blood was positive. The spinal fluid was clear and contained 700 white blood cells per c.mm., 82% of which were lymphocytes. The total protein was 80 mg. per 100 cc. and the spinal fluid Kahn was positive.

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Course. The patient's temperature remained below 99° F. during the entire hospital stay and she improved rapidly with complete recovery from the cranial nerve lesions, without any specific treatment. Following discharge from the hospital, she received 19 injections of mapharsen and 15 of bismuth subsalicylate. In January 1944 the spinal fluid contained no cells, showed a negative mastic, and had 16 mg. of protein per 100 cc., but gave a positive Wassermann in 0.5 cc. of spinal fluid.

Since acute syphilitic meningitis rarely occurs during active antiluetic treatment, the diagnosis of a lymphocytic meningitis which develops during therapy as luetic should be made with extreme caution. Such a diagnosis, however, seems justified in the above 2 cases, because the syphilitic infection was only of several months' duration, and because of the persistence of a positive spinal fluid Wassermann long after other signs of the meningitis had disappeared.

In the first case, the patient was treated with a soluble bismuth compound at the time of onset of the meningeal symptoms. Such preparations of bismuth are rapidly excreted, usually in 48 hours, and when given weekly for cases of early syphilis, constitute inadequate treatment. Although this would explain the appearance of meningitis in the first case, its occurrence in the second patient who received standard treatment is more difficult to understand. Merritt[8] explained such cases as being the result of inadequate treatment for that particular individual, but even the relatively intensive 26-week Army schedule may not protect the patient against developing meningitis.[3]

Papilledema in Syphilitic Meningitis. The occurrence of a severe papilledema in acute syphilitic meningitis has frequently resulted in diagnostic errors. It is easily understood how the presence of choked disks together with other signs of increased intracranial pressure, such as headache, nausea and vomiting, can lead to consideration of an intracranial tumor as the most likely diagnosis. Although these signs of acute hydrocephalus have been repeatedly observed in luetic infections,[1,4,5] they still remain a source of confusion. The following patient, who developed such symptoms after a head injury, is an example of this type of problem.

Case 3. M. J., a 22 year old white female, had been under treatment for early syphilis for 4 months prior to admission and had received regular weekly injections of neoarsphenamine. Eleven days after the last injection, she developed a headache and 2 days after this sustained an injury to the forehead in an automobile collision. This resulted in no loss of consciousness, but in an apparent aggravation of the headache. The patient developed tinnitus and dizziness and noted transitory numbness of the upper extremities. Three weeks after the onset of the illness, her neck became stiff and painful on motion. The headaches became more severe and nausea and vomiting developed.

Because of the emphasis the patient placed on her head injury she was admitted to the surgical service of Grady Hospital with a provisional diagnosis of a subdural hematoma. On admission the patient appeared apathetic but coöperative, and in no obvious distress. There was a definite bilateral papilledema of 1 to 2 diopters. The retinal veins appeared distended in both fundi. There was a mild right-sided facial weakness with some impairment of hearing on the right. The neck was moderately stiff with a positive Brudzinski sign. The heart, lungs and abdomen were negative. The deep reflexes were normal.

Examination of the urine showed nothing abnormal. There were 14 gm. of hemoglobin per 100 cc. of blood, and the leukocyte count was 15,000 per

c.mm. The blood Kahn was positive. The spinal fluid contained 1460 white cells per c.mm., 98% of which were lymphocytes. The spinal fluid protein level was 200 mg. per 100 cc., and the mastic curve was 13331. The spinal fluid Kahn was repeatedly positive.

Course. After the spinal fluid findings were obtained, the patient was transferred to the medical ward. During the first week in the hospital the temperature fell from 102 to 99° F., and the headache cleared considerably although no treatment was instituted. During the second week, mapharsen was given twice weekly with no appreciable change in the patient's symptoms. The headache continued, with some stiffness of the neck, but after 6 weeks she became symptom-free and was discharged. Four months after the onset of the illness, a repeated spinal fluid examination showed 44 mg. of protein per 100 cc., a mastic curve of 442100 and a positive Kahn. The papilledema had completely disappeared and the patient felt completely well.

Recognition of the luetic nature of this patient's illness was obscured by the patient's emphasis upon her head injury. She at first dated all the symptoms to her trauma, and it was only after the spinal fluid report had returned that further questioning brought to light her luetic background and the fact that the symptoms preceded the injury by a few days.

Response of Syphilitic Meningitis to Specific Treatment. One of the most frequently used aids in the diagnosis of acute syphilitic meningitis has been the response to antiluetic therapy. That this criterion may be of little value is evident in Cases 2 and 3, where marked clinical improvement occurred without any specific treatment. In such patients the results of arsenical and bismuth therapy may easily be misinterpreted. Occasionally, however, a definite response to specific treatment can be observed, thus confirming the diagnosis of syphilis. The following patient is an example of the value of a therapeutic trial of mapharsen.

Case 4. P. C., a 23 year old white female, entered the hospital in November 1943 in a completely irrational and stuporous condition. The history revealed that she had become ill 4 weeks prior to admission with a severe frontal headache. This became progressively worse and was associated with nausea, vomiting and earache. The patient consumed large quantities of headache powders for the pain and was also given sulfathiazole without relief. She complained of stiffness of the neck, became very irritable and occasionally lapsed into delirium for periods of 24 hours or more. Two days before admission she became stuporous and was finally admitted in this condition.

It was later revealed that the patient had begun weekly injections, presumably for syphilis, from a private physician several months prior to admission, but received only 4 treatments before becoming delinquent.

On admission the patient's temperature was 103° F. She appeared acutely ill, was irrational, and complained hysterically of headache. The pupils reacted well to light and accommodation. The fundi showed definite edema of the nerve heads bilaterally with some distention of the retinal veins. The other cranial nerves appeared intact. The nose and throat were normal and the neck quite stiff with a positive Brudzinski sign. The chest and heart were normal, the blood pressure 130/70, and the abdominal examination negative. The reflexes of the extremities were active; a bilateral Kernig sign was present.

Examination of the urine was negative. There were 12 gm. of hemoglobin per 100 cc. of blood, with 20,000 white blood cells per c.mm. (97% neutrophils). The blood bromide level was 125 mg. per 100 cc. and the blood Kahn positive. The spinal fluid contained 670 white blood cells per c.mm., 92%

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of which were lymphocytes. The spinal fluid protein content was 200, the chloride 670, and the sugar 52 mg. per 100 cc. The mastic curve was 455551 and the spinal fluid Kahn was positive. Five subsequent spinal punctures revealed essentially the same results with only a small reduction of cells and protein before discharge.

Course. On admission the patient was thought to have meningococcal meningitis and received sulfadiazine with parenteral fluids. In 36 hours the temperature became normal and remained so. She became rational, had less stiffness of the neck and seemed to be remarkably improved. There appeared to be a slight weakness of lateral deviation of the right eye, which cleared in a few days. At the end of the first hospital week it became apparent that the patient had not completely recovered. She complained bitterly of headaches, became irritable and difficult to placate. She cried easily, had numerous aches and pains and was quite fretful. The spinal fluid findings remained the same as on admission, and on the 12th hospital day she was started on daily injections of mapharsen. After the third dose she obtained complete relief from her headache, became cheerful and, except for visual blurring, was entirely asymptomatic. A total of 20 mapharsen and 10 bismuth injections were given in the next 4 weeks, but the patient again became delinquent and has not returned.

In this case there appeared to be some improvement coincident with hydration, bromide excretion and sulfadiazine therapy, but it was not until mapharsen was given that the patient became well.

Not only will cases of syphilitic meningitis improve frequently without treatment, but other types of lymphocytic meningitis may get well coincidently with antiluetic treatment. The course of virus meningitides, for example, is usually quite benign, and the patient may get well at the time he is receiving luetic therapy. In these instances the therapeutic response may be completely misinterpreted. Since syphilitic meningitis is not a rapidly fatal condition, it seems advisable to withhold treatment in undiagnosed cases of lymphocytic meningitis, unless the patient is very ill, in which case a therapeutic trial with mapharsen is justified.

Relation of Meningitis of Spinal Fluid Tests for Syphilis. It has now become well known that a positive spinal fluid Wassermann reaction in a patient with meningitis and systemic syphilis is not diagnostic of neurosyphilis, as an increase of protein in the spinal fluid may carry with it serum reagin.[7] It was for this reason that in the above patients a diagnosis of acute syphilitic meningitis could not be made simply on the basis of positive spinal fluid Wassermann or Kahn tests.

In a highly syphilitic population, therefore, falsely positive spinal fluid Wassermann tests become a not infrequent occurrence. There have been several cases at the Grady Hospital of tuberculous meningitis with persistently positive Wassermann tests and also 1 case of probable choriomeningitis which showed a similar reaction.*

* Since this paper was submitted for publication, a report on biologic falsely positive spinal fluid Wassermann reactions has appeared (Scott, V., Reynolds, F. W., and Mohr, C. F.: Am. J. Syph. Gonor. and Ven. Dis., **28**, 431, 1944). This study showed that falsely positive spinal fluid Wassermann tests may occur in syphilitic and non-syphilitic patients during the course of pyogenic, aseptic, and tuberculous meningitis, and perhaps in other types of intracranial disease. These authors caution against making the diagnosis of neurosyphilis unless repeated spinal fluid examinations, performed after the acute infection has subsided, show the continued presence of reagin.

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Falsely Negative Tests. Not only are falsely positive spinal Wassermann tests seen in non-luetic meningitides, but occasionally falsely negative tests occur in syphilitic meningitis. Extreme caution must be exercised in diagnosing this condition and the following case, which finally developed a positive spinal fluid Kahn after previously negative tests, is an example of this condition.

CASE 5. J. C., a 19 year old colored male, developed a penile lesion in September 1943, associated with a positive serologic test for syphilis. He was then treated with 5 mapharsen injections before becoming delinquent. Early in November 1943, he began having frontal headaches, which gradually became more severe. He noted associated nausea, vomiting and dizziness and was seen in the Out-Patient Department on Dec. 7, 1943. At this time physical examination showed a somewhat lethargic patient with no stiffness of the neck or cranial nerve palsies. The spinal fluid was reported as containing no cells, but since the fluid had been allowed to stand overnight, this count was not deemed accurate. There were 88 mg. of protein per 100 cc. of spinal fluid, the mastic was 110000, and the spinal fluid Kahn test was negative at both the state and hospital laboratories. It was unfortunate that a Wassermann test on the spinal fluid was not done at this time as it may have suggested the correct diagnosis. The patient again became delinquent and did not return until Jan. 17, 1944, when he was admitted to the hospital because of persistent headache, malaise and weakness.

On admission, the physical examination was entirely normal except for a moderate degree of lethargy. No neurologic abnormalities were noted. There were 14 gm. of hemoglobin per 100 cc. of blood, and the leukocyte count was 10,000 per c.mm. The spinal fluid contained 220 cells per c.mm., all lymphocytes, 128 mg. of protein per 100 cc., and the mastic curve was 331000. The spinal fluid Kahn test was now positive and the Wassermann was also positive with 0.125 cc. of spinal fluid.

Course. The patient's temperature never rose above 99° F. and he became completely asymptomatic after the first injection of mapharsen. He was then placed on a tri-weekly schedule of mapharsen and after 10 weeks the spinal fluid was again examined. This time there were 4 cells, 42 mg. of protein per 100 cc., the Kahn and mastic tests were negative, but the Wassermann was positive with 1 cc. and 0.5 cc. of spinal fluid.

Cases of syphilitic meningitis with negative spinal fluid Wassermann tests have been reported,[8,12] but such diagnoses often leave room for doubt. The above case is of interest, therefore, because a positive spinal fluid Kahn finally appeared 6 weeks after negative tests had been obtained in the active stage of the illness. It is well known that the spinal fluid Kahn and Wassermann tests are the last of the spinal fluid tests to become positive in early neurosyphilis.[2] In this case apparently insufficient time had elapsed for a positive flocculation test to develop at the time of the first spinal puncture, even though the patient had meningeal symptoms. With the development of a higher protein level and a first zone colloidal reaction, the Kahn became positive and the diagnosis was established.

In cases such as this, when the spinal fluid Wassermann reaction is negative, a definite diagnosis of syphilitic meningitis can only be established by withholding treatment until the test becomes positive. In the milder cases of meningitis such a practice seems advisable. After the diagnosis has been made, it can be confirmed by repeated examinations of spinal fluid during syphilitic treatment. In meningitis of

luetic origin the cells, protein and mastic usually return to normal levels before the Wassermann reaction becomes completely negative.

Summary. During the past 2 years we have observed 9 cases of acute syphilitic meningitis, 5 of which presented diagnostic difficulties.

Despite the rarity of its occurrence, 2 cases of luetic meningitis appeared during the course of regular bismuth therapy.

Several of our patients with this syndrome responded without syphilitic treatment. Since other types of lymphocytic meningitis may improve coincidently with specific therapy, a therapeutic response to arsenicals is usually of little value, though at times helpful in the diagnosis of acute syphilitic meningitis.

In 1 case of syphilitic meningitis in which there was a history of head trauma, the presence of papilledema was the source of diagnostic error.

In the highly syphilitic population of this region, falsely positive spinal fluid Wassermann tests are not infrequently observed in lymphocytic meningitides. One case of syphilitic meningitis is reported in which a negative spinal fluid test for syphilis appeared after the onset of clinical symptoms. Withholding treatment in such cases seems advisable in order to establish a definite diagnosis of luetic meningitis.

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JOINT DISEASE ASSOCIATED WITH ACROMEGALY*†

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Although Pierre Marie's[5] masterly description of the hypertrophic skeletal changes in the syndrome he named acromegaly was published

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in 1886, nearly half a century elapsed before acromegalic joint lesions became the subject of histologic investigation. To be sure, Llewellyn[4] in 1909 and Oppenheim[6] in 1913 noted gross alterations "similar to arthritis deformans" in the articulations of such patients. However, it remained for Erdheim[2,3] in 1931 to direct attention to the relationship between pituitary tumors and a specific form of articular disease. Unquestionably, the fact that the joint lesions in long-standing acromegaly may be indistinguishable from those of degenerative joint disease[1] delayed the recognition of their specific nature, as was pointed out by Erdheim. In this relatively uncommon syndrome, the amount of autopsy material suitable for the demonstration of early articular changes is small. Insofar as we could ascertain there are no reports of such cases in the English literature. Having had the opportunity to make such postmortem examination of the tissues from an acromegalic who died with bacterial endocarditis, we wish to report the pertinent findings, in order to substantiate Erdheim's thesis in part as well as to stimulate interest in this unusual arthropathy.*

Case Summary. A 58 year old, male, Jewish photo-engraver entered the hospital complaining of severe low back pain of 8 weeks duration. Twenty years before admission, gradual and painless enlargement of the acral parts had begun, but for the last 15 years no appreciable change had taken place. Two months prior to entry, without known cause, the knees became tender, painful on motion and swollen. A severe, dull, bifrontal headache developed soon after and persisted constantly for several days. Within a week there appeared again without any obvious precipitating factor a sharp pain in the back centered in the midline below the scapular angle and extending a few inches to either side. Two weeks preceding admission both legs showed dependent edema. The patient had had moderate polydipsia and nocturia for many years. During the recent illness, he had been orthopneic and had lost about 30 pounds. Over 15 years before entry, he fractured both wrists. The remainder of the personal history was negative for symptoms of previous articular or cardiac disease. The marital and family histories were not remarkable.

Physical examination showed a poorly nourished, weak, elderly male with pronounced acromegalic features and skeletal changes (Figs. 1 and 2). There was no lymphadenopathy. The hair was normal except for frontal baldness. There were no tophi. A few remaining lower teeth showed caries. The mandible, nose and supra-orbital ridges were prominent and multiple exostoses could be palpated over the occiput. There was diffuse tenderness over the skull bones. The conjunctivæ were reddened but showed no petechiæ. Arcus senilis was marked. Both optic disks had indistinct margins and could be visualized only with a −20 lens. The visual fields were normal. The ears were long, the tongue thick, speech clumsy, voice deep. Distinct beading of the costochondral junctions was noted in the barrel-shaped chest. There was enlargement of the right breast. The heart was not definitely enlarged to physical examination, P_2 was louder than A_2, and a blowing systolic murmur was heard diffusely over the precordium. The peripheral vessels were non-resilient, the blood pressure was 120/65. The lungs were hyperresonant, but at both bases dullness and moist râles were noted. The abdomen was markedly scaphoid, the spleen enlarged. Genitalia and prostate were normal.

The spine showed an increase in the cervical and thoracic curves, moderate rigidity and pain on motion. There was tenderness over the spinous processes

* The authors wish to express their appreciation to Dr. Herman L. Blumgart, Physician-in-Chief, Beth Israel Hospital, Boston, for the permission to present the clinical material incorporated in this report.

of the 11th thoracic to the 4th lumbar vertebræ, greatest at the 12th dorsal. The hands and feet were large and spade-shaped and all peripheral joints showed evidence of marked hypertrophic changes. There was wasting of the musculature of the extremities, pitting edema of both lower legs and eczema about the left ankle. Knee jerks and ankle jerks could not be elicited. Neurologic examination was otherwise non-contributory.

FIG. 1

FIG. 2

FIGS. 1 and 2.—The pronounced acromegalic features and skeletal changes exhibited by this patient are well illustrated in these two photographs.

Roentgenograms of the chest revealed emphysematous lungs, tortuosity of the aorta, slight enlargement of the left ventricle and moderate scalloping of the ribs. Films of the skull showed the sella turcica to be enlarged with thinning and slight erosion of the posterior clinoid processes. Roentgenograms of the joints demonstrated flattening of the head of the right humerus, narrowing of the right humeral scapular articulation, widening of its glenoid process and increased density of subchondral bone alternating with cystic areas. Marked marginal hypertrophic changes were observed in the carpal and terminal phalangeal articulations. The intervertebral articulations and vertebral bodies in the dorsal segment of the spine showed massive spur formation. The 6th and 7th thoracic vertebræ had a wedge-shaped appearance and the intervening disk was collapsed in a manner suggesting an old fracture. Laboratory tests showed a diabetic type of glucose tolerance curve; basal metabolic rate up to +57%, not changed after administration of iodine; and a high normal value for urinary calcium by the Sulkowitch test. The serum calcium was 10 mg. per 100 cc., phosphorus 3 mg. per 100 cc. and phosphatase 7.6 units per 100 cc.

The course in the hospital was characterized by rapidly progressive generalized weakness, and irregularly elevated temperature to 102.5° F. in the presence of a low normal white blood cell count and a normal differential. The sedimentation rate was elevated. There was increasing evidence of systemic infection. A loud blowing aortic diastolic murmur appeared while the patient was under observation. Repeated blood cultures were positive for nonhemolytic streptococci. The patient did not respond to sulfonamide therapy and multiple transfusions. He developed microscopic hematuria, the nonprotein nitrogen rose from 25 to 51 mg. %, the respirations became extremely labored and irregular and the patient died on the 47th day after admission.

*Pathologic Examination.** A striking diminution in fatty tissue was noted in the subcutaneous tissues, omentum, mediastinum and all perivisceral areas. In its place, abundant connective tissue of unusual, gelatinous appearance was observed.

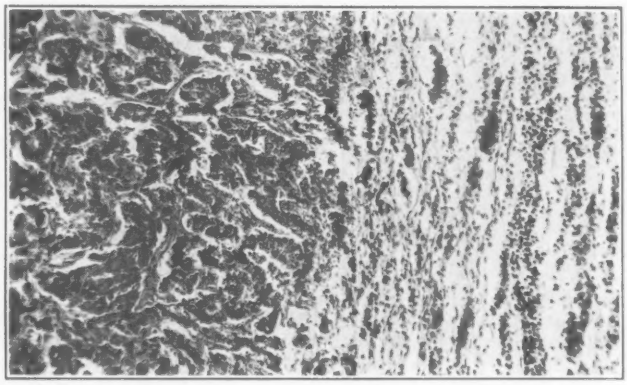

FIG. 3.—The structural and cytologic features of the pituitary adenoma are shown at the left of this photomicrograph (× 85). A margin of the compressed and atrophied gland is shown on the right-hand half of the reproduction.

Apparently due to the kyphoscoliosis of the spine, there had been moderate dextro-rotation of the heart, which was normal in shape but showed hypertrophy of the myocardium and weighed 410 gm. There were many areas of patchy atherosclerosis of the coronary vessels but no occlusions could be seen. The aorta exhibited several atheromatous plaques. Microscopically, the mitral, aortic and tricuspid valves showed changes characteristic of old rheumatic infection. On the mitral and aortic valves were superimposed vegetations consisting of massive clumps of cocci, leukocytes, red blood cells and fibrin and extending deeply into the valve structure. No Aschoff bodies were seen anywhere in the heart. Postmortem culture from the right auricle showed non-hemolytic streptococci and *Staphylococcus albus* after 2 days incubation.

Examination of the lungs gave evidence of moderate congestion and changes consistent with patchy pneumonitis in the right lower lobe. The spleen, weighing 440 gm. was of slightly increased firmness, and showed hyalinization of the centers of some follicles and intimal sclerosis of the larger vessels. The liver weighed 1760 gm. The parenchyma was normal except for moderate congestion about the central veins. The pancreas and kidneys appeared normal. The adrenal glands were slightly enlarged and showed moderate postmortem degeneration of the medullary portion and congestion of the cortex. The prostate gland was markedly enlarged. Its acini were increased

* We are indebted to Dr. Monroe J. Schlesinger of the Beth Israel Hospital for all pathologic interpretations, except for those pertaining to the skeleton, which he kindly placed at our disposal.

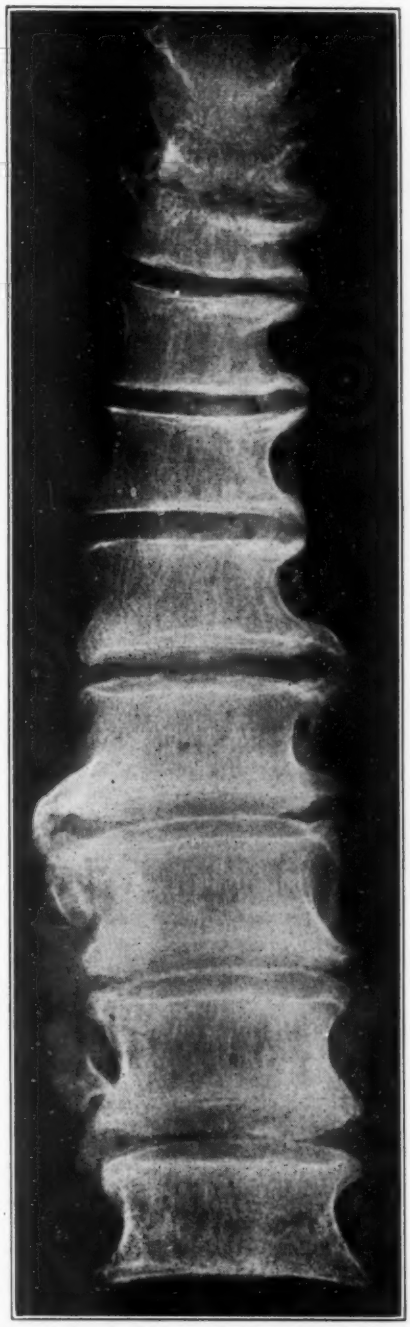

FIG. 4.—Roentgenogram of an excised portion of the spine. Note the marked marginal lipping. The obliteration of the intervertebral disks between the 6th and 7th thoracic vertebræ could be the result of trauma.

in number and of irregular size and shape. They were lined by fairly tall columnar epithelium with basally placed, deeply staining nuclei. The epithelium appeared thrown up into folds, and the intervening fibromuscular material was relatively reduced in amount. The testes showed normal glandular structure and evidence of active spermatogenesis. The thyroid and parathyroid glands exhibited no definite pathologic features. The vocal cords were not remarkable. The dura appeared slightly thickened and edematous. The contents of the cranial vault were not remarkable except for findings relating to the hypophysis.

FIG. 5.—The pronounced widening and irregular ossification of the costochondral junctions are illustrated in these roentgenograms of representative segments.

The enlarged pituitary gland, weighing in excess of 4 gm., projected from the bony fossa. It was found to consist of a well-defined adenomatous nodule surrounded by a fibrous tissue capsule and composed of nests and anastomosing cords of cells in a richly vascular stroma, with ample fibrous interstitium (Fig. 3). The cells were rather large, irregularly rounded and had poorly demarcated borders, a pale pink, finely granular cytoplasm and large, centrally and eccentrally placed, oval, vesicular nuclei, each containing eccentric nucleoli. There were no active mitoses or giant cells. The predominant cellular constituents exhibited an only imperfect resemblance to the eosinophilic cells of the pituitary gland and possessed a cytoplasm which was more granular and more deeply staining than that of the chromophobe cells. At the periphery of the adenomatous nodule, a compressed but otherwise fairly normal appearing anterior lobe was seen, containing preponderantly chromophobe elements but also some poorly staining eosinophilic cells. A small piece of intermediate lobe showed cells whose arrangement tended to be in the form of acini. An occasional dilated acinus was filled with bluish-pink staining material similar in appearance to colloid. An antemortem biopsy specimen from the right breast revealed changes typical of gynecomastia.

There was prominent lateral and slightly less conspicuous anterior lipping of the vertebral bodies at the margins of the disks. The intervertebral cartilages were flattened. The 6th and 7th segments of the thoracic spine were completely fused (Fig. 4). Segments of rib showed well-defined fusiform enlargement of the costochondral junctions (Fig. 5).

FIG. 6.—In this roentgenogram of an excised portion of the femoral condyles of the left knee are shown the hypertrophic changes of advanced degenerative joint disease.

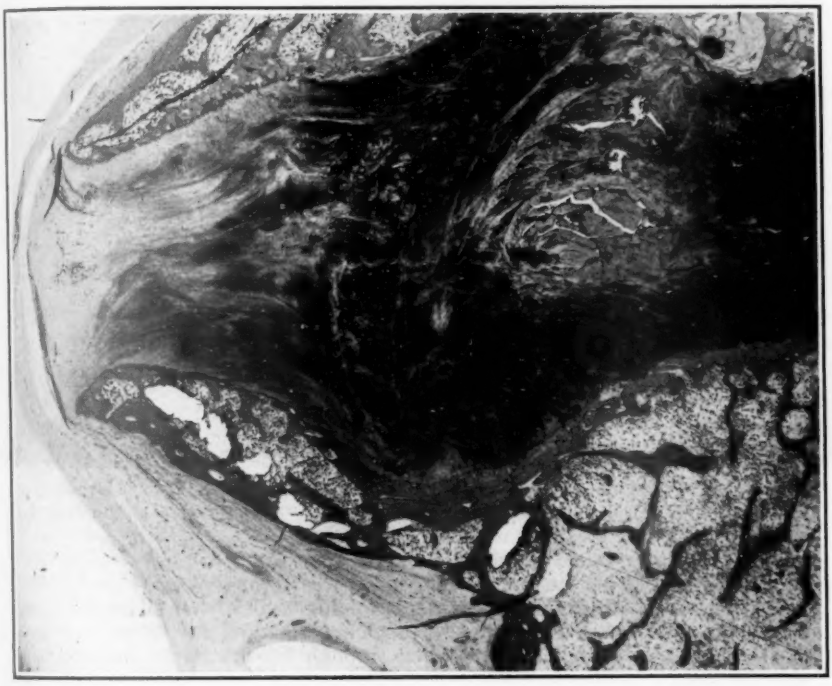

FIG. 7.—Marked bony overgrowth (lipping) about an expanded intervertebral disk. These changes, although very pronounced, are apparently similar to the spinal lesions that are frequently seen in elderly non-acromegalic subjects.

Grossly, the right knee joint showed an extraordinary degree of cartilaginous and bony overgrowth at the perichondral margins (Fig. 6). The articular aspects of the patella and the patellar surfaces of the femur were strikingly irregular. The hyaline covering deeply eroded, the subchondral bone had become exposed on the weight-bearing portions of the femoral condyles. The synovial lining tissue had undergone pronounced villous hypertrophy and, in the fresh state, appeared markedly hyperemic.

Microscopic sections of the intervertebral articulations revealed marked anterior protrusion of the disks and evidence of a severe cataplastic process involving the annulus fibrosus, nucleus pulposus and the cartilaginous plates (Fig. 7). Fibrillation of the hyaline substance, clustering of chondrocytes and mucinoid degeneration of the disk centers with marked fibrosis in the peripheral areas were apparent. Frequent focal deposits of calcium and occasional vascularization extending from the marrow through the calcified layer could be observed. The 5th and 7th disks were greatly narrowed (Fig. 4), and the anterior margins of the vertebral bodies exhibited prominent beak-shaped bony overgrowths, occasionally almost enveloping the protruding disk material. The 6th intervertebral disk had nearly disappeared, leaving only a few circumscribed cartilaginous masses between the bony borders of the adjacent vertebræ.

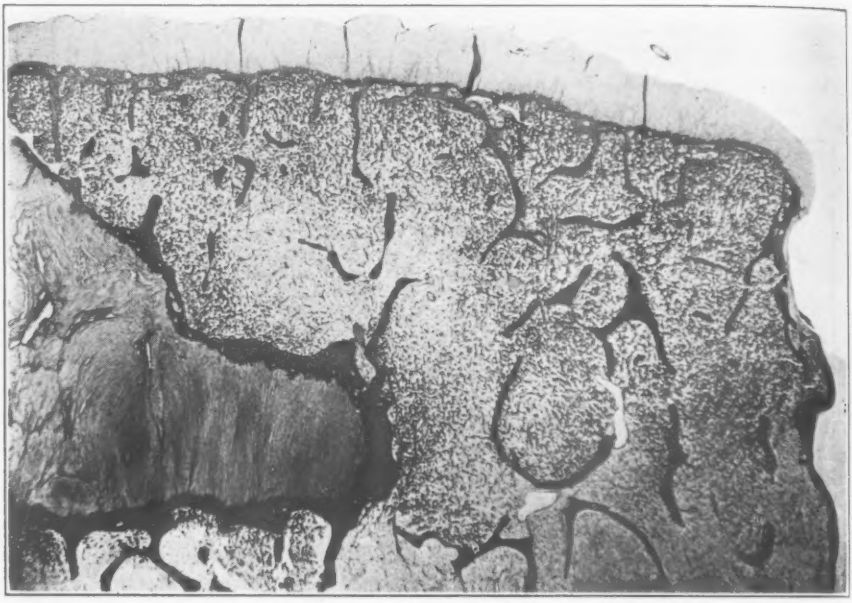

FIG. 8.—An extremely marked marginal overgrowth of bone (× 8) of one margin of the patellar surface of the femur. Pronounced degenerative changes in the articular cartilage are readily seen.

In some regions, patches of condensed, newly formed bone were visible, indicating an active growth process resembling that of a healing fracture. Throughout the sections, wide osteoid seams were noted and tongues of proliferating cartilage frequently extended through the calcified layer into the marrow spaces. Transverse sections of the vertebral bodies and intervertebral articulations from T8 to L2 demonstrated similar alterations. The marginal lipping, however, was more pronounced in the thoracic region than in the lumbar segments and had reached large proportions on the lateral aspects of the vertebræ (Fig. 4).

Sections from the patella, the patellar surface of the femur and from the medial and lateral femoral condyles showed an extreme degree of degenerative change, with cartilaginous and bony hypertrophy (Figs. 8 and 9). Overgrowths at the perichondrial margins measured as much as 2 x 3 cm. and widely overhung the periphery of the cortex. The articular cartilage was markedly fibrillated, the matrix being roughly cleft. The chondrocytes had undergone degenerative and proliferative changes in all layers. The weight-

bearing surfaces of the condyles were, in large areas, made up of condensed subchondral bone devoid of any cartilaginous covering. The synovial membrane of the knee joint was characterized by hypertrophy of the villi which showed a notable increase in fibrous tissue (Fig. 10). Infiltration with chronic inflammatory cells was not a striking feature. A frequent finding in sections from bone marrow and synovialis were large areas of myxomatous degeneration in the fatty and connective tissues (Fig. 10).

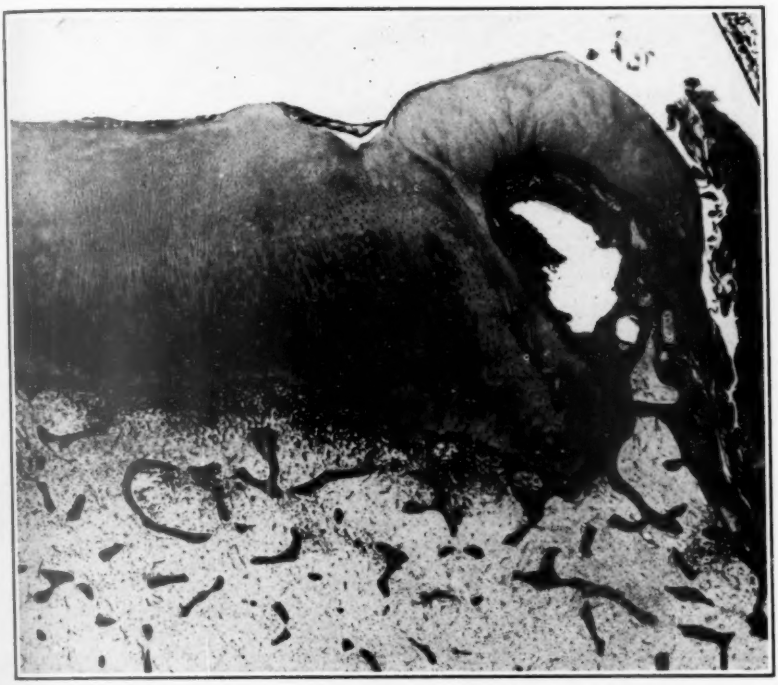

FIG. 9.—Lesions typical of advanced degenerative joint disease are illustrated in this reproduction of a transverse section of one margin of the patella.

Microscopic study of the proximal and distal interphalangeal joints of 1 toe revealed singularly interesting alterations in the hyaline cartilage (Figs. 11 and 12). The calcified stratum was increased in thickness. The lowermost hyaline layer showed an abnormal preponderance of matrix over cells, while in the adjacent zone the cell columns were more prominent and more transversely arranged than in the normal. The individual lacunar spaces contained an excessive number of cells. The layer of columnar chondrocytes was increased in size and there was evidence of active cellular proliferation. It seems important to point out that these changes were not associated with superficial erosion of cartilage, and the usual early histologic manifestations of degenerative joint disease were slight or absent (Fig. 13). However, bony excrescences and tufting were noted about the terminal phalanx.

The costochondral junctions were the site of severe and uncommon pathologic alterations (Figs. 14, 15 and 16). Instead of a nearly linear separation between bone and cartilage, there was a wide and diffuse area of transition which, in contrast to normal, showed considerable enlargement in all dimensions (Fig. 5). The center of the lesion was characterized by an irregular advance of vascular marrow into the chondral part of the rib. Where such

invasion had taken place, there was frequently evidence of active bone formation. Interspersed between the foci of ossification were pleomorphic islands of degenerating and proliferating cartilage. The more recently formed hyaline cartilage located in the peripheral part of the rib likewise showed active proliferation with voluminous cells. The perichondrium had apparently been replaced by a sheath of periosteum and bone, continuous with the osseous shaft of the rib.

FIG. 10.—Synovial tissue of the knee showing mild diffuse inflammatory cell infiltration of the superficial zone. The curious edematous and myxomatous change prevailing in many parts of the connective tissues is indicated in the lower half of the photograph (× 75).

Discussion. To interpret the various findings pertaining to the articular structures in this case, it seems advisable to consider first those lesions which appeared familiar from previous observations. The vertebral column showed gross, microscopic and radiologic alterations, the greater part of which were wholly consistent with degenerative joint disease of the spine and which we were able to match in

most details with material from elderly non-acromegalic subjects. There are, however, three qualifications to this similarity. First, the degree of hypertrophic bone changes at the margins of the intervertebral articulations, as evident in the roentgenogram of the excised

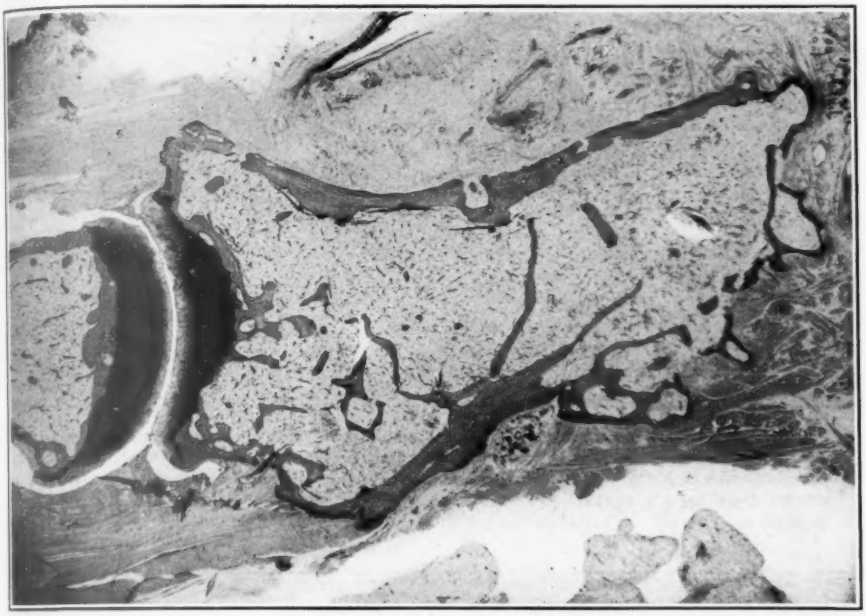

FIG. 11.—A photomicrograph (× 8) of the terminal phalanx and distal articulation of the second toe. Note the irregular bony overgrowth about the end of the phalanx. The articular surfaces show little evidence of degenerative joint disease.

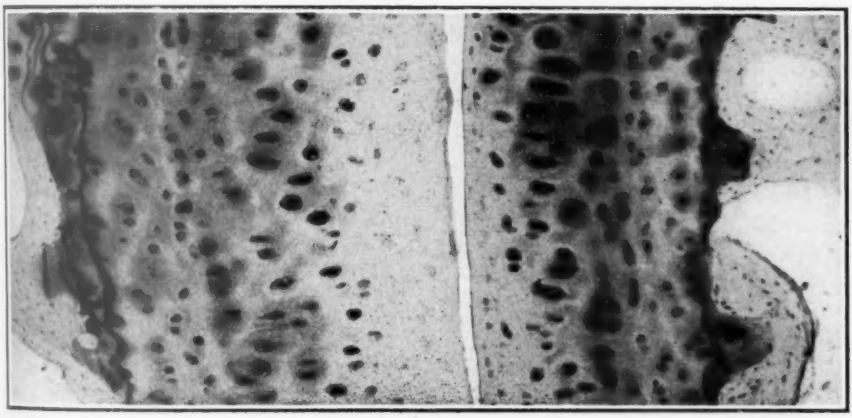

FIG. 12.—Opposing articular surfaces of the terminal phalangeal joint of the toe illustrated in Figure 11 are shown in this photomicrograph (× 75). The deepest third of cartilage shows fewer cell groups than normal. Their distribution, however, is not unusual. In the middle third the cartilage cells are exceedingly numerous and arranged in irregular columns and clusters. The superficial third of each articular surface is normal or shows only minimal degenerative changes.

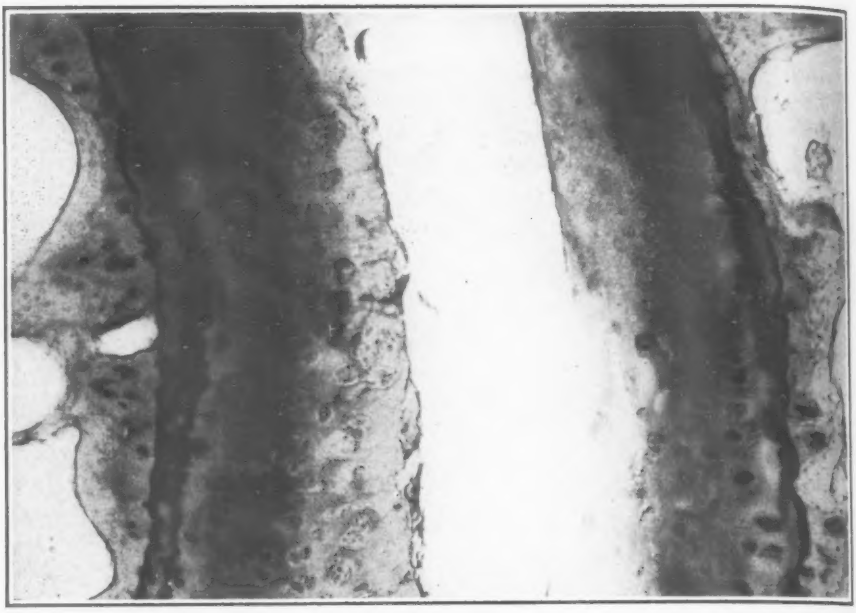

FIG. 13.—A photomicrograph (× 75) of a portion of a terminal phalangeal joint of a non-acromegalic elderly man showing the usual changes of degenerative joint disease. The superficial portions of each cartilaginous surface show alterations, whereas the deeper portions are normal. This photograph should be compared with Figures 11 and 12.

FIG. 14.—A portion of a section of an expanded rib cartilage (see Fig. 5) is reproduced in this photograph (× 8). Note the evidence of active cartilage cell proliferation and the irregular islands of ossification. The segment illustrated was several centimeters distal to the normal costochondral junction.

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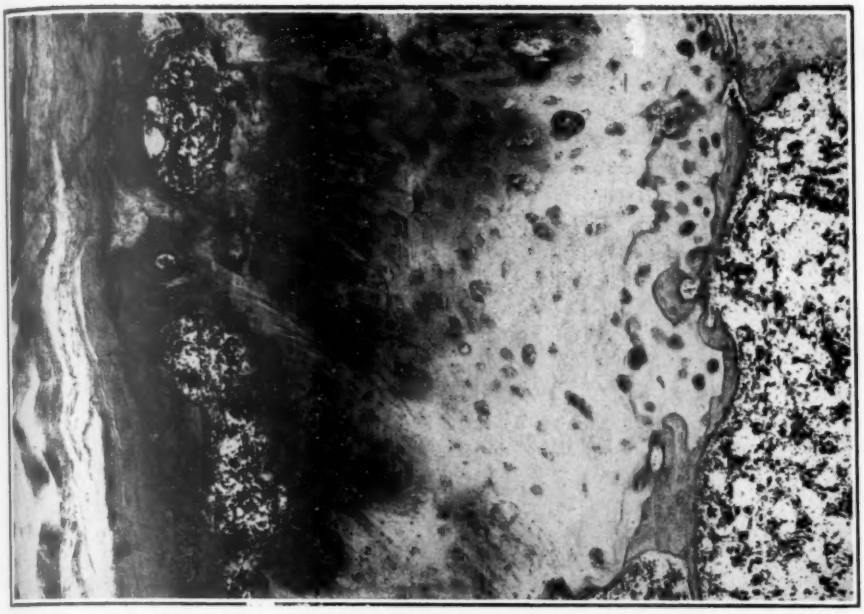

FIG. 15.—Active endochondral ossification is indicated, in this photomicrograph (× 75) of the cartilaginous portion of a rib, by the apparent bony replacement of the transversely placed cartilage cell columns. This reactivation of growth sequences has led to the formation of a bony sleeve around the rib cartilage. To the right of the photograph is an island of fully developed cancellous bone that has replaced the original cartilagenous tissue.

FIG. 16.—A portion of an enlarged rib cartilage is shown in this photomicrograph (× 75). The clustering and immaturity of the cartilage cells is indicative of pronounced proliferative activity. Irregular areas of ossification are apparent.

spine (Fig. 4), is unusually marked. Second, in contrast to the usual relationship, the segments T11 and 12 appeared slightly larger in transverse diameter than the lumbar vertebræ L1 and 2, disregarding, of course, the exostoses. This discrepancy is visible also in the Roent-

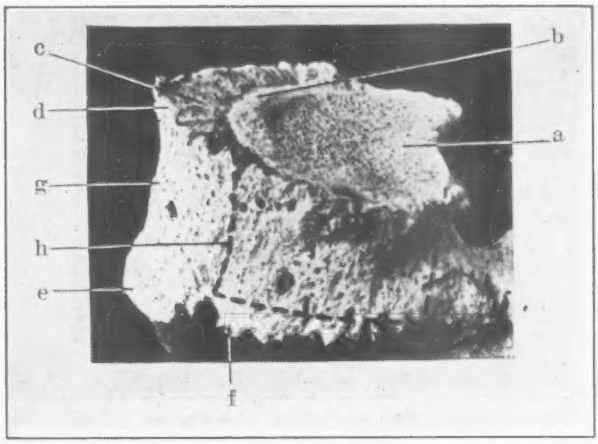

FIG. 17.—Relation of the newly formed bone to the original vertebral body. The lines drawn in the figure show that the perforated surface (*a*) and the edge (*b*) of the old vertebral body are located inside the newly formed bone. The latter has a dented edge (*f*) but shows no exostoses either at (*d*) or (*e*). Like a normal vertebra, it is slightly concave in the front. The old periosteal contour is sunken and runs parallel to the new one. (From J. Erdheim, Über Wirbelsäulenveränderungen bei Akromegalie, Virchows Arch. f. path. Anat., **281**, 197, 1931.)

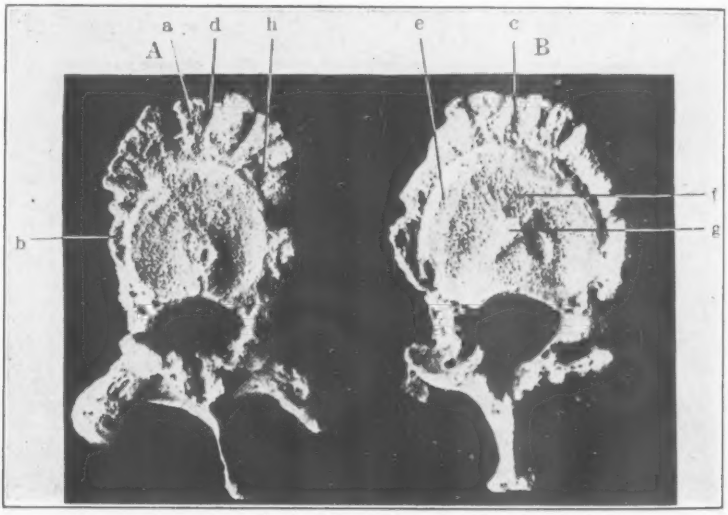

FIG. 18.—Here one notes the diaphyseal origin of the newly added bone on the lower surface of the 3rd lumbar vertebra. The edge of the old vertebral body (*a*) casts the shadow (*c*) on the newly formed bone (*b*), which does not originate from the marginal edge (*d*) but from the periosteal surface of the diaphysis. (From J. Erdheim, Über Wirbelsäulenveränderungen bei Akromegalie, Virchows Arch. f. path. Anat., **281**, 197, 1931.)

gen ray photograph (Fig. 4). Lastly, there was complete and fairly extensive bony union between the dorsal vertebræ, D6 and 7, associated with exceedingly severe degeneration of the intervening disk. Judging from the microscopic appearance, this lesion appeared to be of several months' duration and could not be attributed, either clinically or histo-

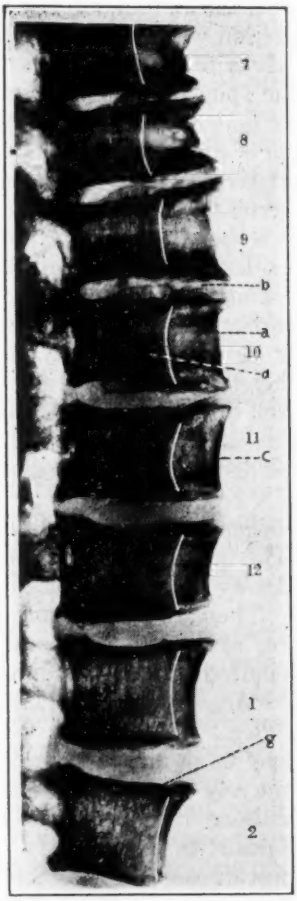

FIG. 19.—Roentgenogram of one-half of the vertebral column, including the 7th dorsal to the 2nd lumbar vertebræ. The white line separates the old vertebral bodies and the newly laid down bone. Contrary to the general rule, the bodies of the lower vertebræ become smaller. However, less newly formed bone is found in the lower vertebræ, thus indicating, as is normally the case, that the original vertebral bodies are larger in the lower portion of the vertebral column. (From J. Erdheim, Über Wirbelsäulenveränderungen bei Akromegalie, Virchows Arch. f. path. Anat., **281**, 197, 1931.)

logically, to an infectious process. Although on careful questioning the patient had denied any pertinent injuries, the lesion may, of course, have been the result of trauma, either alone or as an adjunct in causing a pathologic fracture. Whether the deviations from the common picture of degenerative disease of the spine, noted in this patient,

represent incidental and disconnected findings or are related to the specific articular lesion of acromegaly cannot be decided on the basis of the material in our hands. The latter interpretation would be consistent with the conspicuous evidence of generalized active endochondral ossification in the vertebral bodies. Certainly the vertebral alterations did not approach in appearance the fully developed acromegalic spine lesions which Erdheim found in 1 of the 2 cases he reported.[3]

To facilitate a comparison with the pathologic findings described in this case, Erdheim's description may be summarized briefly. In essence, the acromegalic spine is distinguished by additional growth of the vertebral bodies and of the intervertebral disks. The bony increment develops from the periosteum and by endochondral ossification of proliferating cartilage. It is more evident on the anterior and lateral aspects of the vertebral column than posteriorly (Figs. 17 and 18). The newly formed bone is demarcated, very clearly in the Roentgen ray, and to a lesser extent in microscopic section, by the irregular arrangement and deficient calcification of the trabeculæ (Fig. 19). The new cortex is pathologically wide and the increased transverse diameter of the vertebral body may give the mistaken impression of reduced height. The new disk segment arises from the perichondrium and is well differentiated into the various normal components, including the calcified layer and the hyaline plate. Certain criteria may be used to distinguish between acromegalic and purely degenerative disease of the spine. In the latter, marginal exostoses develop in response to degeneration of the disks and therefore vary in location and degree. The bony new-growths occurring in the former are independent of and may be present without any degeneration of the intervertebral disks. They are more uniformly distributed throughout the vertebral column. It need not be emphasized that both types of lesions may be and indeed have been found in the same patient. Conversely, not every acromegalic individual will show the specific articular changes in all sites.

The lesions observed by us in most of the peripheral joint surfaces examined did not reveal any distinctive features. To be sure, the degree of hypertrophic bone reaction again was striking, but the pathologic process conformed in essentials to the familiar pattern of marked degenerative joint disease. The exception to this was found, however, in the changes in one toe joint, which were inconsistent with the common type of senescent arthropathy but compatible with the changes described by Erdheim.[2] Whereas in the former, the earliest histologic stigmata are swelling and fibrillation of the matrix of the superficial hyaline covering, leading to its erosion and the well-known subsequent alterations in the joint margins, subchondral bone and synovialis,[1] the acromegalic change was found by Erdheim to begin with hyperplasia and hypertrophy of the columnar zone of chondrocytes associated with an increase in matrix.[2] The deepest, calcified layer cannot, in the adult joint, participate in this juvenile type of reaction, although it shares in the relatively slower process of endochondral ossification advancing from the subchondral marrow. This

disparity in reaction, as well as the rapid disorganization of the columnar cartilaginous zone which is primarily responsible for elastic action, renders the articular cartilage vulnerable to functional stresses, subsequently produces clefting and fibrillation and engenders, at last, a pathologic picture identical with that of degenerative joint disease. As Erdheim pointed out, the difference between the two entities is clearly discernible only in their incipient stages. To demonstrate the distinguishing features, we have included the microphotograph of a finger joint from a patient with senescent degenerative joint disease (Heberden's node) (Fig. 13 for comparison with Figs. 11 and 12).

Microscopic lesions, such as those observed in the costochondral cartilages, we could not recall having encountered heretofore. The alterations consist of marked and irregular hyperplasia and hypertrophy of chondrocytes and increase in matrix in the middle cortical portions of the cartilaginous rib. Coupled with these phenomena is a progressive endochondral ossification at the cartilage bone border. The former are responsible for the prominent beading shown in the photograph of the patient and in the Roentgen ray film of the rib specimen (acromegalic rosary) (Fig. 5). The latter results in advance of the vascular bone marrow into the central avital part of the chondral cartilages and in increased periosteal bone formation at the periphery, so that for a short distance, two concentric layers of trabecular bone may be seen to envelop the former cartilaginous cortex (Fig. 14). Thus, nodal as well as circumferential growth has occurred at the cartilage bone border and has led to the abnormal expansion of the thorax, long known as one of the striking characteristics of acromegaly. A comparison between our sections and those shown by Erdheim reveals close similarity in every essential detail.[2]

Conclusion. The gross and microscopic pathologic findings in representative joints of an acromegalic patient have been reported. It was found that in many respects, particularly where there were advanced alterations, the histologic picture closely resembled that of severe degenerative joint disease. In some features and in a few individual sites, however, the changes appeared to be of a wholly different nature and could not be regarded as reactions to primary degeneration of cartilage. These particular phenomena, principally new-growths of cartilage and bone, appeared to indicate reactivation of cartilage growth and enhanced endochondral ossification, unphysiologic at the age of this patient and perhaps the result of a specific hormonal stimulus.

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PROGRESS
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RADIOLOGY

UNDER THE CHARGE OF
HARRY M. WEBER, M.D., AND DAVID G. PUGH, M.D.
SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

NOTES ON A VARIETY OF ROENTGENOLOGIC PROBLEMS

BY HARRY M. WEBER, M.D.

Choledocholithiasis. It has been said[3] that a patient with gall stones has a 13 to 20% chance of having 1 or more stones in the common bile duct. This estimate of the incidence of choledocholithiasis was based on a study of published figures from several large clinics, so it may be regarded as a reasonably accurate one. An unqualified roentgenologic diagnosis of stone in the common bile duct is but rarely made. Since the common bile duct is hardly ever depicted on cholecystograms, the stones it might contain must be of the so-called opaque variety, that is, they must contain an adequate amount of calcium if they are to be depicted on cholecystograms; such stones would be demonstrable roentgenographically without the administration of a cholecystographic medium. Roentgenographic demonstration of so-called non-opaque stones in the common bile duct would require a most fortuitous combination of circumstances; to accomplish it otherwise the common bile duct must be made accessible, by means of choledochostomy, for direct injection with a fluid contrast medium. This procedure is known as cholangiography.

Sahler and Hampton[2] have reported a series of 12 cases in which a preoperative diagnosis of choledocholithiasis was verified at operation. In all instances the stones contained enough calcium to make them demonstrable roentgenographically without the use of a cholecystographic medium. The authors noted that it is not generally appreciated that stones in the common bile duct can be shown in this way presumably because (1) the incidence of choledocholithiasis is relatively low, and (2) when present it is difficult to determine the position of the stones with accuracy. To reveal the stones, the roentgenograms must be of best quality. By means of antero-posterior and lateral projections of a normal cholangiogram, Sahler and Hampton showed that the common bile duct is projected below the lower right ribs, across the upper medial pole of the right kidney, so that its lower end overlies the renal pelvis, and that it occupies the center of the body in the antero-posterior plane. The gall bladder occupies a much more anterior position in the body. When choledocholithiasis is suspected, Sahler and Hampton recommended that stereoscopic or both postero-anterior and lateral roentgenograms be made.

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In the postero-anterior projection shadows of stones in the common duct will be less distinct and more distorted than those of stones in the gall bladder because the latter concretions will be nearer the film. The distinction between renal calculus and stone in the common bile duct is made with the lateral view. In this projection, the stone in the common bile duct lies anterior to the spine, whereas urinary calculi are projected over the spine unless the kidney happens to be dystopic. A stone in the ampulla of Vater might lie far enough posteriorly to simulate a renal stone. In obscure cases, a urographic procedure was required to distinguish between renal stones and stone in the common bile duct. If, in an antero-posterior projection, a stone is shown to be in the immediate vicinity of the duodenum or in the duodenal loop, it will usually prove to be in the common bile duct, since it will then be below the junction of the common bile duct and cystic duct. Sahler and Hampton used this maneuver to distinguish between stone in the cystic duct and stone in the common bile duct and called attention to the development of hydrops of the gall bladder when the cystic duct is occluded by calculus. They encountered no remarkable difficulty in distinguishing choledocholithiasis from other calcified masses in the right upper abdomen, such as calcified costal cartilages, ecchinococcus cysts and calcified abdominal vessels. Choledocholithiasis should be suspected in all cases in which calcification is seen in the region of the gall bladder and common bile duct, in cases in which milk-of-calcium bile is demonstrated, and in cases in which the patients are jaundiced. It seems apparent that with a more extended use of these simple maneuvers the roentgenologic examination can be made to contribute somewhat more than it has in the past to the diagnosis of choledocholithiasis.

Adenoma of the Bronchus. This benign sounding name is applied to a neoplasm which in a strict pathologic sense, at least, is a malignant one. It grows slowly, but it actually invades the bronchial wall; its cells tend to be poorly differentiated and to be arranged in a disorderly fashion. Metastasis occurs, but rarely, and then only after a period of several years. Lowry and Rigler[1] recognized this somewhat anomalous situation, and in a very illuminating and convincing paper they pointed out that bronchial adenoma does not act like the more familiar, because so much more frequently encountered, type of bronchogenic malignant lesion, but like a benign lesion. They emphasized that the disease which adenoma of the bronchus produces has a fairly characteristic clinical pattern of its own, quite different from that of the ordinary run of frankly malignant tumors of the bronchi. They showed that by recognizing this pattern and by exacting the full yield of modern roentgenologic and bronchoscopic techniques including biopsy, the two diseases can quite readily be distinguished from each other, and in relatively early stages. They argued that this differentiation is important, for the adenoma has by far the more favorable prognosis to begin with, and because it is so much less lethal it is probably safe in most instances for the physician to gamble with the less radical therapeutic procedures, and so the ultimate prognosis is still more favorably influenced.

Some of the points Lowry and Rigler made might well bear repetition and reconsideration in these pages.

About 6% of primary tumors of the bronchus are adenomas. This may seem to be a low incidence, but Churchill is quoted to the effect that about a fourth of all resectable tumors of the bronchi belong in this group; therefore, among the curable bronchial neoplasms, adenoma is relatively

common. Almost 80% of patients with adenoma have symptoms before the age of 40, many much earlier than that; 90% of the victims of carcinoma are over 40. Sixty % of bronchial adenomas occur in women; 90% of bronchial carcinomas occur in men. These striking contrasts suggested strongly to Lowry and Rigler that the 2 tumors are fundamentally different and not merely grades or stages of the same kind of neoplasm.

It is generally held that bronchial adenomas originate in the epithelium of the bronchial mucous glands, for they are found practically only in bronchi 10 mm. or more in diameter, where the mucous ducts also occur. This theory of their origin also helps to explain the occurrence, in many of the cases, of extension of the tumor through the bronchial wall beyond the cartilaginous rings, a layer also penetrated by the mucous ducts. Bronchial adenomas are true tumors; they are the cause, not the result, of the inflammatory processes so often seen in association with them. Grossly, they are smooth, round or oval, pink, sessile or pedunculated masses, sometimes extending through the bronchial wall to form extrabronchial portions larger than the intrabronchial. Small, and cuboidal or polygonal in shape, the neoplastic cells tend to be uniform in size and staining properties and to look undifferentiated; they grow in irregular masses and cords, sometimes form acini; mitotic figures are few in number. Growth is slow, but the tumor gradually occludes the bronchus in which it arises, and in this process repeated infections occur aborad to the occlusion. Sooner or later, part of the affected lung is destroyed by recurring infection. Bronchiectasis is almost inevitable, and the more acute infectious processes such as suppurative pneumonia, abscess and empyema may eventually prove fatal.

The history and physical signs depend entirely on the degree of bronchial occlusion which develops and upon the type and extent of the secondary changes which have been produced in the affected lung. Prominent in the histories of the cases are bouts of pulmonary infection, some of which are severe, slow to resolve, and featured by cough, purulent sputum, fever, pleuritis—all occurring repeatedly and obviously arising from the same part of the lung. Between such attacks the patient may be in good health although the cough often persists. The steady downhill course of the disease produced by the frankly malignant bronchial neoplasms is in sharp contrast to the characteristic periods of remission. Hemoptysis occurs at some time or other in two-thirds of the cases. This is often profuse; it tends to start and end abruptly, and seems to accompany the menses in women more often than does hemoptysis from other causes. The cough may be productive or not. Wheezing, cyanosis and dyspnea are observed in advanced cases. Early in the course of the disease there may be no abnormal physical signs; late in the course, the signs are those of total atelectasis. In some of the cases there is clinical evidence of obstructive emphysema; in practically all of them bronchiectasis develops within a year or two after the onset of symptoms.

Roentgenologic examinations have a rôle of first importance in the diagnosis of bronchial adenoma. Cases have been reported in which no abnormal roentgenologic findings could be elicited, but Lowry and Rigler had no such experience and they expressed the opinion that the situation must be exceedingly rare. Roentgenologic diagnostic maneuvers include the standard antero-posterior and lateral projections of the thorax, bronchography, and body-section roentgenography. Atelectasis, total or partial, commonly accompanied by the "drowned lung" phenomenon, is a frequent finding; if intermittent and recurrent, this finding is especially character-

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istic. In other instances the pneumonitis, likewise remittent and recurrent, is the prominent roentgenologic finding, and the pulmonary changes as depicted on the roentgenograms strongly suggest those of an atypical pneumonia. Evidence of bronchiectasis localized to a single lobe should always make the diagnostician think of bronchial adenoma. A mediastinal mass with associated evidence of bronchial obstruction is to be considered as a possible extrabronchial extension of an adenoma of the bronchus. With bronchography it is possible to demonstrate the bronchiectasis and the site of the bronchial obstruction with great accuracy. A "cap-shaped" deformity of the bronchial outline, due to a layering of the opaque oil over the round, smooth, intrabronchial mass, is characteristic. Carcinoma of the bronchus produces a more diffuse elongated "rat-tail" type of deformity of the bronchial lumen. With body-section roentgenography Lowry and Rigler succeeded in demonstrating the intrabronchial mass of the adenoma directly, the air in the bronchus serving as a contrast medium. It was not possible, however, to do this in all instances. They also found repeated roentgenologic examinations of inestimable value in pursuing their studies of their cases.

The final diagnosis of bronchial adenoma is made by bronchoscopic examination at which the gross features of the lesion are characteristic. Biopsy or other instrumentation may cause free bleeding which may be profuse enough to occlude all or a portion of the bronchial tree of the affected side. Lowry and Rigler prefer to let the clot liquefy and be removed by natural processes. Such removal ordinarily takes place within a few days. They warned that attempts at bronchoscopic removal of the clot are often followed by more hemorrhage.

Pathologic diagnosis by means of small sections of tissue removed by bronchoscopic biopsy are reliable, of course, only if actual and representative neoplastic substance is delivered to the pathologist. This is not always possible. In any event, Lowry and Rigler recommended that the diagnosis of adenoma of the bronchus be made to rest on the composite results of clinical, roentgenologic and bronchoscopic examination; if all these are in accord and indicate adenoma, a conflicting pathologic report should not be accepted as the final diagnostic word.

Treatment has been along 3 different lines: Bronchoscopic removal seems to have the most to offer to patients in whom the adenoma is discovered early before it has produced much damage to the lung. This method of treatment is favored, too, if the lesion involves the main bronchus so that pneumonectomy would be required for radical removal, in patients who refuse pulmonary resection, and in those whose tumor is so situated that resection is impossible. Patients who are advised to accept lobectomy or pneumonectomy are also advised to undergo preliminary local removal to provide for optimal preoperative drainage of suppurative areas in the lung so as to minimize the surgical risk. Experience with irradiation is too limited to make a satisfactory estimate of its efficacy. Physicians who have used it most find that bronchial adenomas are somewhat sensitive to irradiation therapy, and further investigation with carefully controlled dosage is in order, It is clear that pulmonary resection with total removal will give the most desirable end-result in the treatment of a neoplasm having the maleficent possibilities this one has, but the risk that has to be assumed is a disturbing feature. Lowry and Rigler hold that each case must be assessed individually with respect to the size, site and extension of the tumor, and the amount of pulmonary damage the tumor has produced. On this basis, they form a rough idea of the patient's

prognosis if the tumor is not removed radically, and against this prognosis they weigh the risk of the procedure considered necessary to extirpate it. A few patients are selected to undergo local removal of the tumor. Since the surgical risk of lobectomy is now so low, they advised this procedure if the adenoma is so situated that it can be removed by lobectomy or combined resection of the lower and middle lobes. Pneumonectomy carries with it a considerably higher surgical risk, so that when this procedure is required Lowry and Rigler prefer to advise bronchoscopic removal and observe the patient for a year or two. If there is no recurrence, and if the symptoms disappear, the patient is merely kept under observation. With rapid recurrence of the tumor, or with persistence of troublesome symptoms, or with evidence of the presence of a large extrabronchial extension of the growth, especially if it is increasing in size, pneumonectomy is reluctantly recommended as the less dangerous of two hazardous alternatives.

With detailed and well-illustrated reports of 7 cases the clinical, roentgenologic and therapeutic features of this most interesting pulmonary disease were exemplified.

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THERAPEUTICS

UNDER THE CHARGE OF
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The Editors regret that through unavoidable circumstances it has become impossible to have a progress article in this department for this number.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MARCH 20, 1945

Studies on the Prolonged Maintenance of Adult Dogs on a Purified Diet. A. O. Seeler and R. H. Silber (Merck Inst. for Ther. Research). Six adult female dogs were placed on a basal diet which according to present knowledge had no significant amounts of vitamin B complex factors. In addition to the fat-soluble vitamins this diet was supplemented with adequate amounts of thiamine, riboflavin, pyridoxine and nicotinic acid. Two of the dogs were also given pantothenic acid. One of the dogs on the pantothenic acid-deficient diet began to lose weight after 7 months and died in the 9th month; 2 remained well until the 15th month when they

too began to lose weight. Their condition 17 months after the beginning of the experiment was critical and they were given pantothenic acid. Their response to the vitamin was prompt and within a month the dogs appeared normal again. One of the 4 dogs on the pantothenic acid-deficient diet showed no gross evidence of disease after $4\frac{1}{2}$ years on the diet. Three of the 6 dogs were still in apparent good health after $4\frac{1}{2}$ years on a diet and supplement containing no significant amounts of biotin, inositol or folic acid complex. While choline was not given *per se*, the diet contained 30% casein and consequently had a relatively large amount of methionine. Hematologic studies and blood chemical determinations failed to reveal any abnormalities in these animals. Kidney function tests were negative. Bromsulfalein retention was, however, somewhat greater than at the beginning of the experiment suggesting moderate liver damage.

Experimental Studies on the Excretion of Neutral Red by the Stomach. R. KOLM, S. KOMAROV, and H. SHAY (Med. Research Lab., Samuel S. Fels Fund). The effect of neutral red on gastric secretion and the mechanism of its excretion by the stomach were studied in acute experiments on 17 dogs and 6 cats. Neutral red was found to act as a mild gastric secretagogue when injected intravenously in doses from 7.5 to 20 mg. per kg. body weight. It produced uniformly a small increase in the rate of gastric secretion as well as an increase in acidity or a diminution of alkalinity. In most experiments there was also an increase in pepsin concentration. These effects especially on the peptic cells were prevented largely by preliminary atropinization and to a lesser degree by double cervical vagotomy. In contrast to the action of atropine upon the neutral red effect upon the peptic cells, repeated large doses of this drug failed to abolish completely the stimulating action on the parietal cells.

Neutral red was not excreted by the pyloric mucosa. Evidence is presented that neutral red is not excreted by either the mucous, mucoid cells or the peptic cells. In atropinized animals, neutral red was absorbed and stored for many hours as a yellow pigment by the parietal cells when these cells were not secreting actively and at a time when neutral red excretion in the urine had already reached very low levels. Subsequent administration of histamine (3 to 6 hours after the injection of neutral red) caused the elimination of large quantities of neutral red with the gastric juice. After histamine, the increase in concentration of neutral red paralleled the acidity and concentration of pepsin. As the histamine action continues, there is a diminution in the concentration of neutral red excreted. This decrease is paralleled by a decrease in the concentration of pepsin even if the acidity and rate of gastric secretion continues to rise. Parallelism between the concentration curves of neutral red and pepsin under these conditions is regarded as an expression of the "washing out" process described by Babkin for the action of histamine upon peptic secretion.

The Mechanism of the Virucidal Action of Ascorbic Acid. MORTON KLEIN (Dept. of Bacteriology, Univ. of Penna.). It has been reported that ascorbic acid is virucidal for the viruses of rabies, vaccinia, poliomyelitis, and influenza virus. Chemical studies of the oxidation of ascorbic acid have revealed that during the Cu catalyzed oxidation of ascorbic acid H_2O_2 is formed. It would seem reasonable to assume that the viru-

cidal action of ascorbic acid may be due to the H_2O_2 formed during the oxidation of the compound.

The PR8 strain of influenza A virus, grown in the allantoic sac of the developing chick embryo, was the test virus and intranasal mouse inoculation was used for indicating viral activity. It was found that 0.05 M ascorbic acid diluted in phosphate buffer, pH 7, inactivated 10 MLD of influenza A virus. Catalase, which is known to specifically inactivate H_2O_2, was found to neutralize completely the action of ascorbic acid. H_2O_2 (0.1%), which approximated the concentration of H_2O_2 produced under the conditions of our experiment by 0.05 M ascorbic acid, also inactivated 10 MLD of influenza virus and this inactivation was completely neutralized by catalase.

It is concluded that the virucidal action of ascorbic acid may be explained as being due to the production of H_2O_2 formed during the Cu catalyzed oxidation of ascorbic acid.

Chemical Structures of Co-factors for Bacterial Viruses. T. F. ANDERSON (E. R. Johnson Research Foundation, Univ. of Penna.). Of a group of 7 viruses* (bacteriophages) active on the strain B of *E. coli*, 2, T4 and T6, are very slowly adsorbed on the host in synthetic ammonium lactate medium. Adsorption of T4 and T6 has been found† to be rapid only in the presence of certain co-factors of which *l*-tryptophane is the most active. Out of 47 other compounds tested with T4, only *dl*-phenylalanine, *dl*-tryosine, *dl*-diiodotryosine, *dl*-Bz-3-methyltryptophane and *dl*-Pr-2-methyltryptophane are active. The inactivity of members of a series of tryptophane analogues and derivatives indicates that for co-factor activity a tryptophane analogue must (1) have an intact α-amino group (indole-3-propionic acid and amino-N-methyltryptophane are inactive); (2) have a free carboxyl group (tryptamine and 3-(3-indolyl)-2-amino-propanol (l) are inactive); and (3) have the *l*-configuration (*d*-tryptophane is inactive). The results suggest that in this case at least the process of adsorption involves something more than the simple fitting of structural parts of virus and host; a chemical reaction involving the co-factor may well have to follow the chance encounters between virus and host for the virus to be adsorbed and initiate its activity on the host.

Drying Penicillin. EARL W. FLOSDORF and STUART MUDD (Dept. of Bacteriology, Univ. of Penna. and F. J. Stokes Machine Co., Phila.). Drying penicillin and drying plasma by sublimation in most respects are similar. The primary differences are (1) penicillin must be maintained at a lower temperature and (2) penicillin is dried in small volume per container.

The actual temperature of drying varies with the degree of purification and is usually on the order of $-25°$ to $-30°$ C. and lower. The reason for this low temperature is primarily not lability, but is because at higher temperature partial softening and consequent frothing under vacuum occurs.

Drying in small bottles causes greater hazard of thawing during the loading and evacuation of the drying chambers. For this reason, the

* Demerec, M., and Fano, U.: Genetics, **30**, 119, 1945.

† Anderson, T. F.: J. Cell. and Comp. Physiol., **25**, 17, 1945.

chambers are arranged for chilling to freeze the penicillin after loading but before evacuation.

Penicillin may also be dried in bulk and transferred subsequently to ampoules. This method has not met with favor because it is difficult to make bacteriologic sampling representative and there is less certainty of sterility.

Penicillin may also be dried as a liquid at about room temperature in a few minutes by means of dielectric heating at radio frequencies. Because of rapidity of drying there is no loss in potency even at the higher temperature. In order to prevent frothing of the material from ampoules, the bottles are rotated at high speed according to a method developed by Radio Corporation of America. The centrifugal action holds the penicillin solution next to the walls of the ampoules until drying is completed.

The required degree of final moisture is controversial because insufficient data have been accumulated until now. However, a moisture content of about 0.5% is best for greatest certainty of preservation, this allowing some margin for increase during distribution to the market.

BOOK REVIEWS AND NOTICES

MEDICO-LEGAL BLOOD GROUP DETERMINATION. By DAVID HARLEY, M.D., B.Sc., F.I.C. From the Laboratories of the Inoculation Department, St. Mary's Hosp., London, England. Pp. 119; 13 figs.; 23 tables. Second impression. New York: Grune & Stratton, 1944. Price, $3.50.

THIS little book is a summary, by a British author, of the human blood grouping tests. Emphasis is placed on their application to the problems of disputed parentage and blood and secretion stain identification. The book is divided into 3 main sections. The first part considers the A-B-O and M-N blood types and their heredity. In the second part apparatus and techniques are discussed. The last section is devoted to the history of the application of these tests to medico-legal problems, most examples being drawn from the English courts. The author pleads for legislation enabling the English courts to order the performance of these tests. Let us hope his plea will be heard in the United States, where only a few of the "more enlightened" states (New York, Wisconsin, Ohio, Maine, New Jersey, South Dakota, and Maryland) have adopted adequate legislation.

There is no mention of Rh blood typing. It is true that as yet Rh tests have had almost no application in the courts. However, as they will undoubtedly be used more and more as a supplement or as a check of the other major grouping tests, some mention should have been made. As a summary, this volume makes easy and rapid reading, but it is of course not to be considered as a substitute for the standard reference works. W. S.

THE EXPERIMENTS OF NATURE AND OTHER ESSAYS. Porter Lectures, Series XII. By IRVINE MCQUARRIE, PH.D., M.D., Department of Pediatrics, Univ. of Minnesota. Delivered at the Univ. of Kansas School of Medicine. Lawrence, Kan.: Univ. of Kansas, 1944. Price, $1.00.

THE first of these 3 essay-lectures, titled with a happy phrase from Osler, declares that the intelligent study of sick patients will sometimes uncover new physiologic principles of a sort which might never enter the purview of investigators working with normal experimental animals. Clinicians therefore should study completely all curious phenomena observed at the bedside, utilizing the rich library and laboratory facilities this country's hospitals so bountifully provide. This thesis is more than adequately proved by descriptions of a half-dozen unusual metabolic disturbances, with illuminating expositions of the contribution to medical progress each one exemplifies. The second essay presents a series of brilliant case studies illustrative of the variety of disorders resulting from dysfunctions of the adrenal glands in childhood. The final essay recounts interesting experiences with parasitic, nutritional, and other oriental diseases encountered by the author while serving as visiting professor of pediatrics at Peiping Union Medical College in besieged China during 1939–1940. This small scholarly volume should be read by all pediatricians and internists who desire to keep abreast of the advances in our understanding of unfamiliar and esoteric diseases. I. W.

TRICHINOSIS. By SYLVESTER E. GOULD, M.D., D.Sc., Pathologist and Director of Laboratories, Eloise Hosp., Eloise, Mich.; Assistant Professor of Pathology, Wayne Univ. Coll. of Med., Detroit. Pp. 356. Springfield: Thomas, 1945. Price, $5.00.

Trichinella spiralis, like lice and itch mites, is dependent for its maintenance in man and in swine upon certain rather firmly established patterns of human

behavior. And mankind being what it is, the parasite apparently has little need for concern over its future. For so long as feeding uncooked garbage to swine is profitable, and pork from this source brings a good price, trichinosis will certainly occur. Over the past century, since the parasite was first recognized, it has stimulated a considerable number of publications, for trichinosis should interest the clinician, the pathologist, the geologist, the epidemiologist, the swine grower, the veterinarian and the meat packer, and on occasion has been the subject of international controversy. Dr. Gould has prepared an excellent review of this extensive material. The subject matter is presented under the following chapter headings: I. Historical; II. Life Cycle; III. Morphology; IV. Epidemiology; V. Trichinosis in Animals; VI. Pathology; VII. Immunology; VIII. Laboratory Diagnostic Methods; IX. Symptomatology; X. Diagnosis; XI. Treatment; XII. Prognosis; XIII. Control Measures. The book is well written, excellently pointed and illustrated. It can be recommended without reservation. Both author and publisher are to be congratulated. H. R.

PATIENTS HAVE FAMILIES. By HENRY B. RICHARDSON, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Cornell Univ. Med. Coll.; Attending Physician, New York Hosp.; Visiting Physician, Bellevue Hosp. Pp. 408. New York: The Commonwealth Fund, 1945.

DURING the recent decades American medicine has been fundamentally changed by the rapid expansion of medical knowledge and technique, great improvement of medical education and extensive development of hospitals, laboratories, and facilities for research. These changes have such obvious advantages for the medical profession in the study and treatment of disease that little consideration has been given to the disadvantages they might bring to the patient. It is true that the older generation sometimes bemoaned the disappearance from urban life of the family physician, and it became fashionable for doctors to talk about the importance of treating the patient rather than his organs. However, in the present era of "hospital medicine" not much was done to bring the patient as a person out of his relative obscurity. Recently, however, interest has grown in the social aspects of illness and medical educators and some practitioners have begun to realize that the mind, the emotions, and the environment of patients deserve greater consideration and study, if medical practice is to render the type of service that the people of this country should receive.

The book "Patients Have Families" is representative of this awakening. It is based upon an intensive coöperative study of the families of patients, directed by a physician, the author, with the participation of a psychiatrist, a social anthropologist, and the directors of a medical social service, a family social service, and an educational nursing service. The author has drawn also from his own experience as a physician.

In the first part, families are described and discussed as the unit of illness. An interesting concept of "family equilibrium" is presented which sets forth the various social and emotional forces within the family that determine its characteristics and its relations to illness.

The second part is entitled "The Family as the Unit of Treatment." The life of a true family physician is described, followed by a discussion of the responsibility of the physician to the family and the value of coöperation of psychiatrist and physician. The family is then considered from the point of view of the family case worker, the medical social worker, and the public health nurse.

In the third part, entitled "Present and Future," the family in war time is discussed, and is then considered in its relation to hospital practice and to medical teaching with a final discussion of the family unit as a subject of research. In a long appendix the method of study is described and the various professional techniques that were used are exemplified.

The book contains much that is valuable and interesting and is perhaps a

unique contribution to medicine. It suffers, however, from poor organization and fails to give concrete ideas in regard to some of the topics with which it deals. It is at times tedious and involved and is not easy reading, although it deals with material of human interest that has been thoroughly and competently studied and is brightened here and there by the author's sense of humor. A good many examples of faulty hospital practice are discernible in the accounts of the treatment of patients composing the families that are discussed, and no doubt these faults were a factor in stimulating the intensive study that was carried on for 2 years.

The title of the book is evidence that the author believes that the medical profession needs to be reminded of this fact. He emphasizes the importance of giving consideration to the patient not only as a total individual, but also as to his social setting, and shows how the interplay of forces within the family which constitute family equilibrium may be poorly balanced and thus become a fundamental factor in the cause and maintenance of illness. Unless this factor is included in the consideration of illness, medical care, especially in hospital practice, may be frustrated. G. R.

POET PHYSICIANS. An Anthology of Medical Poetry Written by Physicians. Compiled by MARY LOU MCDONOUGH. Pp. 210. Springfield, Ill.: Thomas, 1945. Price, $5.00.

AN anthology that includes in 200 pages the writings of more than 100 medical poets, extending over 1000 years (nearer 2000, if the translation of Lucretius is included), must indeed have taken the compiler through many libraries in a search extending over a number of years. Beginning with Wang Wei (699–759) of the T'ang Dynasty (whose 2 little gems are, to be sure, not medical poetry), the anthology takes us to the 16th century with but two stops—the well-known "The Salerne School doth by these lines impart all health to England's King" (ca. 1101), and an excerpt from Fracastoro's "Syphilis." In the next 2 centuries, the British dominate—here we find such well-known writers as Cowley, Garth, Arbuthnot, Smollett, Akenside, Goldsmith, Erasmus, Darwin, together with Redi and Schiller. With John Kearsley Mitchell and Walter Channing, Americans make their appearance; from then on they are more than twice as numerous as all the rest. We find no explanation of this obvious disproportion; nor can we agree with a number of Mrs. McDonough's selections which serve chiefly to sustain the quotation from Dr. John Fallon that much of the poetry written by physicians is "poetry in quotation marks and much of it is feeble stuff." Not that there is nothing worthy in these later selections. One misses Zinsser's exquisite sonnet "Now is death merciful," but one finds much to support Merrill Moore's assertion that most of the best poems in the tradition of medical literature are included. The Index of Authors is followed by a longer Cumulative Index of Poet Physicians. This contains many persons whose work one would have liked to have seen included: Aurelianus, Avicenna, Bartholinus, Claude Bernard, Gentile, Haller, Harvey, Helmont, Hippocrates, Imhotep, and so on. But perhaps when much that is good has been provided, it is unseemly to express a wish for more.

E. K.

NEW BOOKS

Manual of Clinical Mycology. Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. By NORMAN F. CONANT, PH.D., Assistant Professor of Bacteriology, Duke Univ. School of Medicine, and Mycologist to Duke Hosp. *et al.* Pp. 348; 148 figs. Philadelphia and London, Saunders, 1944.

Neuro-ophthalmology. By DONALD J. LYLE, B.S., M.D., F.A.C.S., Lecturer on Neuro-ophthalmology, Department of Anatomy, Medical College of the Univ. of Cincinnati; Attending Ophthalmologist to the Good Samaritan Hosp., Christ Hosp., Jewish Hosp., St. Mary's Hosp. and Children's Hosp. Pp. 398; 7 charts; 529 ills. Springfield: Thomas, 1945. Price, $10.50.

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Poet Physicians. An anthology of Medical Poetry Written by Physicians. Compiled by MARY LOU MCDONOUGH. Pp. 210. Springfield: Thomas, 1945. Price, $5.00.

Immuno-catalysis. By M. G. SEVAG, PH.D., Assistant Professor of Biochemistry in Bacteriology, Department of Bacteriology, School of Medicine, Univ. of Pennsylvania, Philadelphia. With a Preface by STUART MUDD, M.A., M.D., Professor of Bacteriology, School of Medicine, Univ. of Pennsylvania, Philadelphia. Pp. 272. Springfield: Thomas, 1945. Price, $4.50.

Modern Methods of Amputation. By EDMUNDO VASCONCELOS, Professor, Univ. of Sao Paulo. With an Introductory Survey of The Development of Amputation by MAJOR GEN. NORMAN T. KIRK, M.C., Surgeon General, U. S. A. Pp. 253; 258 figs. New York: The Philosophical Library of New York, 1945. Price, $10.00.

Marihuana Problems in the City of New York. Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana. Pp. 220. Lancaster: The Jaques Cattell Press, 1944. Price, $2.50.

The Neurologist's Point of View. Essays on Psychiatric and Other Subjects. By I. S. WECHSLER, M.D. Pp. 251. New York: Fischer. Price, $3.00.

Microbial Antagonisms and Antibiotic Substances. By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers Univ.; Microbiologist, New Jersey Agricultural Experiment Station. Pp. 350; 34 figs. New York: The Commonwealth Fund, 1945. Price, $3.75.

The March of Medicine. The New York Academy of Medicine Lectures to the Laity, 1944. Pp. 121. New York: Columbia Univ. Press, 1945. Price, $1.75.

An Introduction to Somatic Methods of Treatment in Psychiatry. By WILLIAM SARGANT, M.A., M.B. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp., and ELIOT SLATER, M.A., M.D. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp. Pp. 171. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

The Chemistry and Physiology of Hormones. Publication of the American Association for the Advancement of Science. Edited by FOREST RAY MOULTON. Pp. 243. Washington, D. C.: American Assn. Advance of Sci., 1944. Price, $3.50 ($4.00).

Trauma in Internal Diseases. With Consideration of Experimental Pathology and Medicolegal Aspects. By RUDOLF A. STERN, M.D., Assistant Attending Physician, City Hosp., New York City. Foreword by FRANCIS CARTER WOOD, M.D., Director of Laboratories and Radiotherapy Department, St. Luke's Hosp., New York. Pp. 590. New York: Grune & Stratton, Inc., 1945. Price, $6.75.

NEW EDITIONS

Tropical Medicine. By SIR LEONARD ROGERS, K.C.S.I., C.I.E., LL.D., M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., Major-General, Indian Medical Service, Ret.; Late Medical Adviser to the India Office, and Physician and Lecturer, London School of Tropical Medicine; Lecturer on Tropical Medicine, London School of Medicine for Women; Late Professor of Pathology, Medical College, Calcutta; and SIR JOHN W. D. MEGAN, K.C.I.E., B.A., M.B., HON. D.SC. (Queen's University, Belfast), Major-General, Indian Medical Service, Ret.; Late Medical Adviser, India Office and Lecturer, London School of Tropical Medicine; Formerly Director-General, Indian Medical Service; Formerly Director and Professor of Tropical Medicine, Calcutta School of Tropical Medicine and Hygiene. 5th Ed. Pp. 518; 2 colored plates and 87 text-figures. Baltimore: Williams & Wilkins, 1944.

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Clinical Roentgenology of the Digestive Tract. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, Univ. of Maryland; Assistant in Gastroenterology, Mercy Hosp.; Consulting Roentgenologist, Sinai Hosp. 2nd Ed. Pp. 769; 550 figs. Baltimore: Williams & Wilkins, 1945. Price, $7.00.

Approved Laboratory Technic. By JOHN A. KOLMER, M.S., M.D., DR. P.H., Sc.D., LL.D., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple Univ.; and FRED BOERNER, V.M.D., Associate Professor of Clinical Bacteriology, Graduate School of Medicine and Assistant Professor of Bacteriology, School of Medicine, Univ. of Pennsylvania; Bacteriologist, Graduate Hosp., Philadelphia. 4th Ed. Pp. 1017; 336 ills. New York: D. Appleton-Century, 1945. Price, $10.00.

This well-known comprehensive text on clinical laboratory methodology has been heavily revised by the authors and four of their thirty collaborators. The general plan remains the same as previous editions. This edition appears at an opportune time to complement Dr. Kolmer's new (1944) "Clinical Diagnosis by Laboratory Methods" which is chie y interpretive. A Spanish language edition of this revision is said to be in preparation.

Textbook of Anæsthetics. By R. J. MINNITT, Trinity College, Cambridge, M.D. (LIVERPOOL), D.A. (R.C.P. and S. ENG.), Lecturer in Anæsthesia, Univ. of Liverpool; and JOHN GILLIES, M.C., M.B., CH.B. (EDINBURGH), D.A. (R.C.P. and S. ENG.), Consultant in Anæsthetics, Department of Health for Scotland. With a chapter on Local and Regional Analgesia by L. B. WEVILL, M.B., F.R.C.S. (EDIN.), Major, R.A.M.C. 6th Ed. Pp. 487; 199 figs. Baltimore: Williams & Wilkins, 1944. Price, $7.00.

Textbook of Abnormal Psychology. By ROY M. DORCUS, Associate Professor of Psychology, Univ. of California at Los Angeles; and G. WILSON SHAFFER, Dean of the College of Arts and Sciences, Lecturer in Psychology, Professor of Health and Physical Education, Johns Hopkins Univ. 3rd Ed. Pp. 547. Baltimore: Williams & Wilkins, 1945. Price, $4.00.

Constitution and Disease. Applied Constitutional Pathology. By JULIUS BAUER, M.D., Professor of Clinical Medicine, College of Medical Evangelists, Los Angeles; Formerly Professor of Medicine, Univ. of Vienna. 2nd Ed. Pp. 255; various ills. and diagrams. New York: Grune & Stratton, 1945. Price, $4.00.

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